SCIENTIFIC DISCUSSION

1. Introduction

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries that is characterised by vascular proliferation and remodelling. It results in a progressive increase in pulmonary arterial resistance and, ultimately, right ventricular failure and death. A diagnosis for primary (or idiopathic) pulmonary hypertension is made when no known risk factor is identified. The functional classification of PAH[1] is as follows:

- Class I: PAH without a resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near-syncope.
- Class II: PAH resulting in a slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near-syncope.
- Class III: PAH resulting a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near-syncope.
- Class IV: PAH resulting in an inability to carry out any physical activity without symptoms. The patient has signs of right heart failure. Dyspnoea, fatigue, or both may be present even at rest, and discomfort is increased by any physical activity.

No current treatment cures this rare, devastating condition. However, during the past years treatment options for patients with the disease have evolved to help prolong their survival and improve their quality of life. At present, conventional treatment for patients with primary and secondary PAH includes calcium-channel blockers, anticoagulants, diuretics and oxygen. In addition, an oral endothelin-1 receptor antagonist (bosentan), an intravenous prostacyclin (epoprostenol), an inhaled prostacyclin (iloprost), a subcutaneous prostacyclin (treprostinil) and a phosphodiesterase-5 inhibitor (sildenafil) have also been licensed for the treatment of PAH in various European countries. Of these, bosentan (Tracleer®), iloprost (Ventavis®) and sildenafil (Revatio®) have been authorised through the centralised procedure for orphan medicinal products, the latter of which received a positive CHMP opinion recently (July 2005). Bosentan is indicated for patients with primary and scleroderma-associated PAH, iloprost only for patients with primary PAH, and sildenafil for patients with primary and CTD-associated PAH. All these three medicinal products are only licensed for patients with NYHA/WHO class III disease severity. As a last resort, a lung or heart/lung transplant may be offered to the patient.

The present application for marketing authorisation of Thelin is made under Article 8.3 (i) and concerns a new active substance, sitaxentan sodium, for which a complete dossier has been submitted. Sitaxentan sodium is an endothelin receptor antagonist (ETRA), with higher selectively for the ET_A receptor than the ET_B receptor subtype.
The approved indication at the recommended dose of 100 mg once daily is for the "Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease."

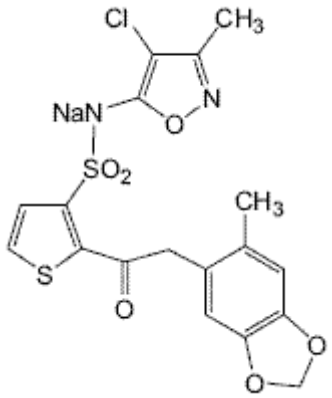
2. Quality aspects

Introduction

[1] This classification was modified from the New York Heart Association classification of patients with cardiac disease. It is adapted from the executive summary of the World Symposium on Primary Pulmonary Hypertension in Evian, France, in 1998.

Thelin is presented as film-coated tablets containing 100 mg sitaxentan sodium INN per tablet. The tablets are packed in PVC-Aclar/Alu blisters or white HDPE bottles with white PP child resistant closure.

Drug Substance (to be changed in the EPAR to "Active Substance")
Sitaxentan sodium is a yellow powder, which is non-hygroscopic. The aqueous solubility is pH dependent, being more soluble in alkaline solution. (0.4 mg/ml at pH 1, rising to 77.8 mg/ml at pH 10). Log P is in the region of 2.



- Manufacture

A four-stage synthetic process has been well described and the critical parameters and accompanying in process controls have been defined. Specifications and control methods of the three main starting materials are satisfactory.
Evidence of the molecular structure of the active substance routinely produced by the defined method of synthesis has been provided in the form of a number of techniques including sodium identity, ICP-OES, ROI, elemental combustion analysis, melting point, IR, UV, ^{1}H and ^{13}C NMR, and high resolution MS.

The organic impurities arising from the defined synthesis are known. The impurities have been identified when found above 0.10% and some below that level. No inorganic impurities are known to be present, and residual solvents are present at levels complying with ICH limits. All lots/batches of sitaxentan sodium used for clinical drug supply have shown a consistent impurity profile, qualified with reference to toxicology studies. In recent batches, no impurities are found above 0.15% by the commercial manufacturing process, so qualification was not necessary (early batches used in toxicity and carcinogenicity studies had levels above 0.15%).
There are 2 degradation products found, which have also been identified as metabolites.

- Specification

The specification includes tests for assay (HPLC), identification (HPLC, FT-IR), total and specified impurities (HPLC), particle size (Lased diffraction), residual solvents etc. The limits as set for the individual impurities are in line with the ICH requirements and in line with recent batch analysis results. Batch used during pre-clinical studies have similar impurity profiles but with slightly higher levels, thus the potential toxicity of the impurities has been appropriately studied in view of the proposed specification and the proposed dose.
Analytical control methods have been validated with regard to relevant guidelines.

- Stability

Batches have been studied at 25ºC/60% RH, 30ºC/65% RH, 40ºC/75% RH, 5ºC., for up to 2 yrs (25ºC) by validated stability-indicating methods.
The active substance is photostable. Standard stress studies have been performed, and the HPLC method has been shown to be stability indicating.
Results support the proposed retest period.

Medicinal Product

- Pharmaceutical Development

The crystalline, stable, non-hygroscopic form of sitaxentan is used, which has a pH dependent aqueous solubility, and the properties are well defined.

The particle size is controlled for uniform dissolution properties and more uniform bioavailability. It has been demonstrated that sitaxentan sodium tablets of two different particle size distributions give comparable dissolution profiles, and all batches have satisfactory content uniformity.

Excipients interactions with the active substance were studied. Excipients that promoted degradation of the active substance were excluded. Also the coatings were tested, and shown to be compatible with sitaxentan sodium. No novel excipients are used. All excipients comply with the PhEur requirements where necessary.

Excipients of human or animal origin:
The only material of human or animal origin is lactose, and is certified to meet EU requirements on TSE. Magnesium stearate and stearic acid are not of animal origin.

- Manufacture of the Product

Sitaxentan sodium 100 mg coated tablets are made from a common granulation procedure. The intragranular components are granulated in a fluid bed granulator, followed by milling, blending with the extragranular components, and compression. The tablet cores are then film-coated for moisture protection and taste masking.

- Product Specification

The product specification is standard for tablets, and contains tests with suitable limits for identity of active substance, assay, dissolution, uniformity of dosage units, total and specified degradation products, water content and microbial bioburden .
Batch analytical results (n=25) indicate satisfactory uniformity and compliance with the agreed specification.

- Stability of the Product

Batches have been studied under the following conditions, 25ºC/60% RH, 30ºC/65% RH, 40ºC/75% RH, Photo stability, Freeze thaw thermal cycle, according to ICH guidelines.
Validated, stability-indicating methods have been used and the results support the shelf life and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

Satisfactory documentation has been provided to confirm the acceptable quality of this medicinal product, and no major objections have been raised during evaluation. The drug substance is adequately characterized and the specification is acceptable in view of the route of synthesis and the various ICH guidelines. The solid drug substance is stable with respect to degradation.

Concerning the finished product, it has been developed in a sound way and the manufacturing process is well studied and controlled. The in-process controls and release specification guarantee consistent control of product quality. The drug product is shown to be stable and to maintain important quality characteristics within the storage time and conditions as defined in the SPC.

Overall the product should perform well in a uniform manner in the clinic.

At the time of the CHMP opinion, a number of minor quality issues related to stability (mass balance) were unresolved.
The applicant agreed to solve these as Follow Up Measures, within an agreed timeframe.

3 Non-clinical aspects

Introduction

Sitaxentan sodium is a highly selective endothelin A (ET_A) receptor antagonist that has been developed for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity.

Endothelin-1 (ET-1) is a potent vascular paracrine and autocrine peptide whose actions are mediated through ET_A receptors present on smooth muscle cells and endothelin B (ET_B) receptors present on endothelial cells. Predominant actions of ET-1 binding to ET_A receptors are vasoconstriction and vascular remodeling, while binding to ET_B receptors results in ET-1 clearance and vasodilatory and antiproliferative effects due in part to nitric oxide and prostacyclin release. ET-1 concentrations are elevated in plasma and lung tissue of patients with PAH. ET-1 and ET_A receptors play a key role in regulating vascular resistance in the lung by directly stimulating vasoconstriction and pulmonary vascular remodeling and this ultimately leads to progressive right heart failure.

The safety and potential local and systemic adverse effects of sitaxentan sodium were evaluated in single- and repeat-dose toxicity studies in mice, rats, and dogs. Reproductive and developmental toxicology studies in rats assessed potential adverse effects on libido, sexual activity, fertility, pregnancy, embryo-fetal development, and post-natal development. The potential carcinogenic risk to humans associated with chronic sitaxentan sodium treatment was evaluated using Sprague-Dawley rats and p53+/mice, as well as the International Committee of Harmonization (ICH)-recommended test battery of genotoxicity studies, which included in vitro assessments of mutagenic activity in bacteria and mammalian cells, clastogenic activity in mammalian cells, and a bone marrow micronucleus assay in mice. Animals of all species were observed for clinical signs, laboratory findings and post-mortem evidence of adverse events in toxicity studies.

All pivotal toxicity studies on safety pharmacology and toxicology were conducted in compliance with Good Laboratory Practices (GLP) Regulations. In addition, non-GLP studies were also conducted. The non-GLP conditions of these studies were not considered to compromise the scientific integrity or affect the experimental results.

Pharmacology

- Primary pharmacodynamics

Sitaxentan sodium is a highly selective ET_A receptor antagonist that has been developed for treatment of PAH. It binds to and blocks selectively (ratio $ET_{A/B}$ is ~6,500 fold) and competitively ET_A receptors with high affinity (K_i 0.43 nM), and potently inhibits receptor signalling (K_i 0.43 nM; 0.686 nM). Tested metabolites show much lower affinity. Animal studies (using rats and pigs) have shown that sitaxentan sodium (mg/kg range) is effective for pulmonary hypertension (PAH) in response to

hypoxia; sitaxentan sodium was effective given (i.v. or oral) either before or after hypoxia. Systemic haemodynamics were not affected.

- Secondary pharmacodynamics

Cardiac effects associated with chronic hypoxia-induced hypertension (increases in pulmonary arterial pressure, pulmonary arterial wall, thickness in right heart hypertrophy) were attenuated by sitaxentan. The ability of sitaxentan sodium to prevent changes in left ventricular function and cardiopulmonary haemodynamics was shown in pigs with cardiopulmonary bypass. Also, sitaxentan treatment blunted the rise in pulmonary vascular resistance without significantly affecting systemic perfusion pressures or heart rate. Its preclinical efficacy was demonstrated in models of heart failure (50 mg/kg/day oral or 20 mg/kg IV: lowering resting mean blood pressure and heart rate) and myocardial infarction (attenuation of rightward shift in left ventricular end-diastolic and end-systolic pressure-volume relationships relative to sham-operated controls, reduced contractile response to norepinephrine in aortic rings as well as reduced systemic haemodynamics).

- Safety pharmacology programme

The potential for sitaxentan sodium to interact with biologically important targets and cause potential adverse side effects was evaluated *in vitro* and *in vivo* in multiple pharmacodynamic animal models of PAH and congestive heart failure (CHF) and cardiovascular, respiratory and central nervous system (CNS) safety pharmacology studies using rats, mice and dogs.

These studies suggest that sitaxentan sodium does not pose a risk of producing adverse effects on respiration, heart rate, blood pressure, action potential prolongation or QT interval, or arrhythmia activity. Detailed studies on potential effects of sitaxentan on the renal, gastrointestinal and respiratory system in different species showed no major side effects.

- Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies have been conducted on sitaxentan sodium, this is acceptable as these studies are planned as post-authorisation commitments.

Pharmacokinetics

Many in vitro studies and in vivo toxicokinetic studies were performed. These data give a good picture of the pharmacokinetics of sitaxentan at high doses in mice (100-400 mg/kg/day), rat (10-120 mg/kg/day) and dog (10-120 mg/kg/day). However, no kinetic information is available for lower dosing of sitaxentan, i.e. for human application a dose of 100 mg/day (≈ 1.4 mg/kg/day) is indicated.
Intestinal absorption of sitaxentan was good, and sitaxentan was not a substrate for P-glycoprotein. Kinetics was generally less than dose-proportional in mice and rats, and dose-proportional or more than dose-proportional in dogs. After dosing of sitaxentan the highest levels of radioactivity were recovered in the liver, and to a lower extent in the kidney and lung. Sitaxentan was highly bound to plasma proteins, i.e. about 99.5% in humans at the C_{max} level (10 µg/ml). Sitaxentan and its metabolites are weak or potent inhibitors of CYP2C9, CYP2C19, and CYP3A4 activity, and possibly of CYP2C8. Sitaxentan may induce enzymes responsible for its own metabolism. Sitaxentan is eliminated via hepatic and renal clearance.
In vitro and in vivo studies on the interaction of sitaxentan with the hepatic transporter proteins (hNTCP (SLC10A1), OATP1B1, OATP1B3, ABC efflux-transporters) are planned and will be provided as a Follow Up Measures.
The safety regarding the metabolite in fraction P8 is not known. In the preclinical testing program, animals (mouse, rats, dogs) have been exposed to the metabolite in fraction P8, but with a very low safety margin. This means that if there is any toxicity associated with P8, there is a risk on an effect in human at therapeutic exposure. To shed light on this point, the metabolite in fraction P8 should be

identified and it should be shown whether or not this metabolite is pharmacologically active. This information will be provided as a Follow Up Measure.

Toxicology

- Single dose toxicity

The acute toxicity of sitaxentan was determined by the oral, i.v. routes of administration in mice and rats. In mice, the highest non-lethal doses were in the 800 to 1200-mg/kg range by the oral and 200 to 300 mg/kg by the intravenous route. In rats, these values were in the range of 500 to 750 mg/kg and 125 to 375 mg/kg/day, respectively. At the maximum tolerated doses, tremors, subdued behaviour, hunched appearance; laboured breathing and hypothermia were observed.

- Repeat dose toxicity (with toxicokinetics)

Repeated dose toxicity of sitaxentan was evaluated orally in mice, and both orally and intravenously in rats and dogs. Three oral toxicity studies of 14-days, 28-days and 26 weeks duration were conducted in mice, four oral toxicity studies with durations of 7 days, 4 weeks, 13 weeks and 26 weeks in rats, and six oral toxicity studies with durations of 3 days to 39 weeks were conducted in dogs. Each study, except the 7-day study in rats, the 3- and 9-day study in dogs included satellite groups in which systemic exposure to sitaxentan was evaluated relationship, to dose level, sex, and duration of dosing.
In general, exposure increased with increasing dose level using once-a-day (QD) dose regimens. There was little evidence of accumulation at doses below 300 mg/kg in mice and 80 mg/kg in dogs with QD dosing. However, some accumulation was observed in rats at dose, greater or equal to 120 mg/k/day and mice at doses ≥ 400 mg/kg/day. In repeat dose oral studies using a two-times-a-day (BID) dosing regimen, substantial accumulation was noted, especially in the trough plasma sitaxentan concentrations of rats at doses of 30 mg/kg BID and above and in dogs at 50 mg/kg BID. This continuous and relatively high exposure most likely accounted for the greater toxicity observed with BID dosing. A BID dosing regimen was less well tolerated than QD administration. As assessed in the 39-week dogs study, the local and systemic effects of sitaxentan were reversible within 12 weeks after dosing stopped.
In mice, rats and dogs, there were changes in a number of haematology parameters (e.g. decreases in Hb and Hct, and increases in platelet count, activated partial thromboplastin times (APTT) and/or prothrombin times (PT). In mice, the slightly longer APTT in males (at all dose levels) and in females at ≥200 mg/kg/day were not associated with any signs of coagulopathy. Increases in APTT were also seen, but coagulopathy (bleedings) were not observed. In rats and dogs, blood-loss anaemia and evidence of multi-organ haemorrhage was noted at higher dose levels in many repeat-dose studies especially with BID dosing. In both rats and mice, there is an association of sitaxentan dose with increased coagulation time parameters which results in safety margins relative to therapeutically effective free plasma concentrations of > 40. In mice rats and dogs, there is no correlation between increases in PT, APTT and platelet count. The dose-dependent increase in PT and APTT observed in vivo, most prominently in rats, indicates that sitaxentan can affect both the intrinsic (APTT) and extrinsic (PT) pathways. In vitro, sitaxentan affected platelet aggregation in human and rat platelet-rich plasma at > 300 and 1000 µg/ml, respectively. Sitaxentan at up to 1000 µg/ml did not alter PT or APTT. Therefore, sitaxentan had minimal effects on coagulation parameters and platelet aggregation in in vitro studies.
In rats and dogs, lower RBC count, Hb concentration and Hct and/or spleen weights were observed. The NOAEL for these effects was ≤20 mg/kg/day in the 13 week- and 30 mg/kg/day in the 26-week rat study, and <10 mg/kg/day in the 39-week dog study.
In mice, rats and dogs, there were changes in a number of clinical chemistry parameters (e.g. decrease in total protein, albumin and/or decreases in creatinine and blood urea nitrogen) and greater heart (most likely mild myocardial hypertrophy). Urinalysis revealed increased urinary water excretion, reflected in greater urine output and/or decreased urine concentrations of potassium and other electrolytes. These observations were considered to be physiological response to plasma volume

expansion. The NOAEL for these effects were <200 mg/kg in mice (28-day study) and <10 mg/kg/day in rats (26-week study) and dogs (39-week study).
In mice, rats and dogs, there were dose-related increases in the weights of liver (centrilobular hypertrophy and occasionally also necrosis). At high doses, gall bladder hyperplasia and/or inflammation were occasionally seen in mice at ≥ 400 mg/kg/day (28-day study) and in dogs at 80 mg/kg/day (39-week study). In the 99-week rat carcinogenicity study, liver hypertrophy was present at an increased incidence in males at 15 mg/kg/day and in females in the 40 and 80 mg/kg/day dose groups. In this study, centrilobular necrosis was present in both sexes at all dose levels. This finding was dose-related and was considered the cause of death in animals at the higher dose levels (≥40 mg/kg/day). The NOAEL for the liver effects were <200 mg/kg in mice (28-day study) and <10 mg/kg/day (26-week study) or <15 mg/kg/day in rats (99-week study, see chapter on carcinogenicity) and 10 mg/kg/day in dogs (39-week study). From these data, safety margins <41.2 (based on the 13-week rat study) and <27 (based on the 99-week rat study) and <3.9 (based on the 39-week dog study) can be calculated. This means that, with respect to early changes in liver weight the safety margin for human is low.
In mice, rats and dogs, decreased serum cholesterol (mice, rat,), triglyceride (rat), bilirubin (rat), and decreased or increased in alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase. The NOAEL for these effects were <100 mg/kg in mice (28-day study) and <10 mg/kg/BID in rats (26-week study) and <10 mg/kg/day in dogs (39-week study).

- Genotoxicity

The Ames test was negative. The mouse lymphoma test was equivocal associated with cytotoxicity and lacking dose dependence. The chromosome aberration test in CHO cells was positive associated with cytotoxicity. The in vivo mouse micronucleus test and the transgenic bioassay in p53± mice were clearly negative. The conclusion that the effects seen in the in vitro studies in mammalian cells have to be regarded as probably biologically irrelevant. This conclusion is further supported by the also negative long-term carcinogenicity study in rats.

- Carcinogenicity

The carcinogenic potential of sitaxentan was seen in a 99-week rat study and in a 26-week study in p53+/- mice.
In the 99-week oral rat study, no toxicokinetic measurements were performed in control animals. However, data do not indicate towards contamination of control samples. Most obvious effects occurring already at low dose (exposure approximately 14-57x human exposure) were haemorrhages in several organs and liver hypertrophy and centrilobular necrosis. The latter effect could possibly be secondary to haemorrhages, but a primary effect of sitaxentan on the liver cannot be ruled out. Red blood cell decreases were probably caused by the haemorrhages. Nasal cavity epithelial degeneration and regeneration occurred, for which a gavage effect is a likely explanation. In males, also already at the lowest dose, atrophy of the seminiferous epithelium in the testis was observed. These effects were not considered relevant by the MAH but nevertheless increased from the low dose were adrenal cortical hyperplasia and degeneration of the lumbar spinal cord nerve fibre in males and cysts in ovary and uterus in females. At the highest dose, body weight and food consumption were decreased and accumulation of macrophages was observed in the lungs.
In male rats, an increased number of benign pheochromocytoma was observed in the adrenals. Benign pheochromocytoma is common in Sprague Dawley rats, however the difference in incidence with controls was quite obvious. The highest incidence of benign pheochromocytomas in male Sprague Dawley rats from the historical control data was 24 %, compared to 18, 21 and 22 % for the 15, 30 and 60 mg/kg sitaxentan treated dose groups. Therefore, based on the historical control data, the incidence of adrenal benign pheochtomocytomas in male Sprague-Dawley rats did not seem to be related to sitaxentan.
Tumour incidences that reached statistical significance in the rat carcinogenicity study were squamous cell carcinomas in males, and basal cell adenomas and keratoacanthomas in male rats. The incidence of squamous cell carcinomas in male rats (up to 5 %) was higher than that of the historical control data

(up to 1.8 %). The incidence of basal cell adenomas in male rats (up to 6.7 %) was higher than that of the historical control data (up to 2.7 %). The incidence of keratoacanthomas in male rats (up to 11.7 %) was below that of the historical control data (up to 13.4 %). The apparent increased skin tumour incidence seems not to be associated with sitaxentan treatment based on the statistical analysis of combined skin squamous cell tumours (papillomas, keratoacanthomas and carcinomas) and combined skin basal cell tumours (adenomas) and absence of phototoxicity. It is not possible to combine all types of skin tumours for statistical analysis in order to elucidate a possible relationship to treatment.
In the 26-week study in p53+/- mice, administration of sitaxentan sodium up to 200 mg/kg/day did not result in increased mortality or clinical signs of toxicity. Weight gain and food consumption were inhibited in males from 50 mg/kg/day (exposure approximately 28-43 x human exposure) and in females from 100 mg/kg/day. Centrilobular hepatocellular hypertrophy in the liver was found in all sitaxentan-treated groups and the incidence was dose-related. Furthermore, in the liver, mononuclear cellular infiltrate, cytoplasmic vacuolization of hepatocytes (males only) and individual cell necrosis (females only, not dose-related) were observed in the liver. The liver effects were probably due to adaptive response to metabolic events in the liver. Degenerative changes of the olfactory epithelium, often associated with the presence of exudates in the nasal cavity, were also observed in sitaxentan sodium treated animals at all dose levels and were considered to be associated with reflux of the test article from the nasopharynx up into the nasal cavity. Furthermore, mononuclear cell infiltrate was observed in the salivary glands of all sitaxentan-treated groups. The number of tumours was not increased in sitaxentan-treated groups. In mice treaded with p-cresidine, the expected transitional cell hyperplasia, metaplasia, papillomas, and/or carcinomas were observed, demonstrating the validity of the model. The combined incidence of papillomas and carcinomas was 66.7% in males and 46.7% in females.

- Reproduction Toxicity

Fertility studies were conducted in rats with sitaxentan at doses up to 120 mg/kg/day (orally). No effect on male fertility was observed. In the female fertility study, maternal no-effect level was considered 20 mg/kg/day by the Applicant because of a very slight effect on weight gain between GD 6-13 at dosages ≥ 80 mg/kg. However, this effect was hardly noticeable and therefore we consider the maternal NOEL in this study to be 120 mg/kg. The incidence of foetuses with the minor abnormality of protrusion of the median liver lobe with thinning diaphragm tended to be increased at ≥ 80 mg/kg/day. However, since the animals were dosed only up to GD6, this could not have been a treatment-related effect. It can be concluded that this study showed no effect on female fertility.
The effect on embryo-foetal development has been investigated rats only. Sitaxentan has demonstrated to affect foetal development at all dose levels with a dose response relationship. Considerable teratogenicity was observed, in particular incomplete soft palates and large additional ossified areas in the skull. At the lowest dose of 20 mg/kg BID, decreased pup survival, delayed female sexual maturity and tubular atrophy/aplasia in the testis were observed. At higher dosages, of F1 animals, weight gain during lactation was decreased, an increased liver was observed in males, male sexual maturity was delayed, auditory function was delayed, and in F1 females a decreased number of implants was observed. At the lowest dose of 20 mg/kg/BID, the exposure to sitaxentan was about 30 times higher than that in healthy and PAH patients. Since lower doses have not been tested, it is not clear whether there is a safety margin for human. It also not clear whether the teratogenic effects observed represent a class effect of endothelin receptor antagonists. Thus far, Bosentan is the only registered ET receptor antagonist. Available preclinical information is insufficient to compare the reproduction toxicity findings of sitaxentan with those of bosentan. There are no data on the use of sitaxentan in pregnant women, but there is a need to treat hypertensive women of child bearing potential, also in situations when other treatment alternatives are not suitable. Following with these data the discussion scheme in the Discussion Paper on Contraindications in Pregnancy, it is concluded that sitaxentan should not be contraindicated in pregnancy.

- Juvenile toxicity:

Sitaxentan sodium is not recommended for use in children under the age of 12 years. A study in juvenile animals is currently performed (results available in 2006), but no clinical studies in children are ongoing at present. The MAH will perform a paediatric clinical programme as a post-authorisation commitment.

- Local tolerance

The local tolerance of orally and IV administered sitaxentan sodium was evaluated as part of the local and systemic toxicity studies. With orally administered sitaxentan sodium, the only evidence of local adverse effects was the occurrence of nasal discharge/epithelial degeneration (secondary to dosing solution reflux) in mice and rats and vomiting in dogs at high doses in a few repeat-dose studies. Since no irritation of GI tract was seen, these findings are not considered to imply that orally administered sitaxentan sodium would produce locally mediated adverse GI effects in humans.
For intravenous administration to mice, rats, and dogs, sitaxentan sodium was dissolved in a vehicle composed of PVP:PG:water (5/10/85, w/v/v) or saline. In mice, sitaxentan sodium caused local irritation at injection sites at ≥ 200 mg/kg with single IV doses. In rats, single or repeated daily IV doses produced local irritation at dose levels ≥ 30 mg/kg/day, characterized by dark and swollen tails. In dogs, repeated daily IV doses produced local irritation at ≥ 10 mg/kg/day, characterized by injection-site inflammation and pain on injection. These findings suggest that sitaxentan sodium does have the potential to cause local irritation at injection sites when administered parenterally.

- Other toxicity studies

Immunotoxicity
During the repeated-dose toxicity studies and the carcinogenicity study performed with sitaxentan, there were no treatment-related effects on haematological parameters (except on red blood cells), serum globulins and immune system organ weights or histopathology. The thymic atrophy observed in mice and dogs was attributed to stress. No cause for concern regarding a possible immunotoxic effect of sitaxentan was revealed.

Phototoxicity
According to the "Note for Guidance on Photosafety testing", photosafety testing is warranted for those chemicals that absorb light in the wave length of 290-700 nm and are either topically applied or reach the skin following systemic exposure (CPMP/SWP/398/01). Sitaxentan is a yellow powder, which indicates that it absorbs light in the visible area. According to the MAH, preliminary in vitro findings using the 3T3 NRU PT phototoxicity test utilizing the permanent mouse fibroblast cell line Balb/c 3T3 do not point to a phototoxic effect. The MAH has agreed to provide a copy of the final study report for the study LOG0001 ("Neutral Red Uptake Phototoxicity Assay of Sitaxentan Sodium in 3T3 Mouse Fibroblasts") as part of the post authorization commitments. The final study report is awaited for assessment.

Ecotoxicity/environmental risk assessment

No ecotoxicity/environmental risk assessment (ERA) has been performed as the current Draft "Note for Guidance on the Environmental Risk Assessment" waives the need for ERA in orphan drugs.

4 Clinical aspects

Introduction

The clinical program included 3 placebo-controlled studies (FPH01, FPH02, and FPH04), 2 open-label studies (TBC11251-211 and FPH03), and 3 long-term extension studies (FPH01-X, FPH01-XC,

FPH02-X). Long-term data were also provided by FPH03, which included de novo subjects as well as extension subjects from FPH04 and FPH06. Additionally, a definitive corrected QT interval (QTc) study (FNL13) and 1 blinded study of 2 doses of sitaxentan in a special population of subjects who were identified as bosentan treatment failures for either efficacy or safety reasons (FPH06) have been conducted.

Three different formulations were used during the development program. The BE-part of study FNL01 (Group A) failed to demonstrate bioequivalence of the two uncoated 50 mg and the coated 100 mg tablets. These results may not be of clinical relevance for the 100 mg coated tablets, which have been found to be clinically effective in the pivotal study and FPH02.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The pharmacokinetic program of sitaxentan sodium consisted of 23 studies, which included 522 patients with PAH. Additionally population pharmacokinetics analysis was conducted using data from 5 Phase 1 studies (FNL01, FNL02, FNL06, FNL08A, and FNL13) and 2 Phase 3 studies (FPH01 and FPH02).
In vitro human biomaterial studies for sitaxentan evaluated its intestinal permeability, protein binding, hepatic metabolism and its potential for metabolism-based drug-drug interactions

- Methods

Sitaxentan concentrations in human plasma were determined by HPLC coupled to a tandem mass spectrometry detector ((LC/MS/MS). The method (low and high concentration range) was developed by Inveresk, Scotland, and then adapted by Analytical solutions Inc, Sunnyvale, USA. After acquisition of Analytical Solutions by MDS Pharma Services, the method was transferred and revalidated at the MDS laboratory in Québec, Canada. Validation reports were submitted and the assays were considered appropriate. The within-run and between-run accuracy and precision values were generally within 10%. The detection of sitaxentan was in the range of 0.2 to 50 µg/ml and 50 to 12000 µg/ml for the Inveresk method. The analytical range was 0.5 to 20000 µg/ml for the Analytical Solutions/MDS method. Sitaxentan is stable in plasma over a period of at least 692 days. Freeze/thaw cycles did not influence the accuracy or precision. Even though no cross reference between the methods performed by the different institutes was performed; the pharmacokinetic results between the studies using the same dosages of sitaxentan are comparable

- Absorption

In vitro studies indicate that sitaxentan is not a substrate of P-gp. Clinical interaction studies indicate that sitaxentan might be a substrate of the OATBP1B1 transport protein.
The absolute bioavailability is between the 70 and 100 %. After administration of 25 and 100 mg coated tablets the median T_{max} ranges from 0.5 to 4 hours. The single-dose mean C_{max} values at the proposed therapeutic dose of 100 mg once daily were in the range of 7-13 µg/mL. At steady state, the mean ± SD C_{max}, C_{trough}, and AUC_{0-24} values were 13 ± 5 µg/mL, 0.06 ±0.07 µg/mL, and 40 ±26 µg.h/mL, respectively (fasting state). Based on C_{max} data, steady state was reached after 5 days in healthy volunteers.
Food affected the C_{max} (43 % decrease with food) and T_{max} (2-fold increase with food) of sitaxentan (100 mg coated tablet) but not the AUC. This food interaction has no clinical implication based on

efficacy data taken at through and close to the C_{max}.. Therefore, it is agreed that sitaxentan can be administered with and without food.

- Distribution

Sitaxentan binds extensively and dose-independently to human plasma proteins (99%), at clinical relevant concentrations. Sitaxentan does not penetrate into erythrocytes. In pre-clinical studies it was shown that sitaxentan is excreted in breast milk. Sitaxentan seems to cross the placenta and blood-brain-barrier.

- Elimination

The terminal half-life after single dose and steady state administration of 100 mg sitaxentan was approximately 7 hours. The terminal half-life did not differ substantially between the different dosages or between oral or intravenous administration. However, at a dose of 1000 mg at steady state the terminal half-life increased to 13 hours. Sitaxentan is metabolised by CYP2C9 and 3A4/5. There appears to be sufficient redundancy in the CYP metabolising pathways so that no single CYP is considered rate limiting. Excretion in the urine and faeces accounted for 55% and 41% of the dose of radioactivity, respectively, for an essentially complete recovery of ~96% after 96 hours. A total of 1 % of the administered drug was excreted unchanged (in urine). The major metabolites of sitaxentan have no clinical relevant activity.

No ADME data were provided in relation to relevant polymorphisms of the drug metabolizing enzymes (e.g. CYP2C9 and CYP2C19). According to the applicant sitaxentan sodium appears to be a substrate for multiple efflux transporters in the canalicular membrane, including MXR and MRP2. The applicant commits to conduct, and provided some preliminary data on preclinical in-vitro studies to investigate the interaction of sitaxentan with several hepatic transport proteins (OATP, the human hepatic ABC efflux transporters MRP2 (ABCC2), MXR (ABCG2/BCRP), and BSEP (ABCB11/sPgp)). A statin interaction study using pravastatin is also planned to evaluate co-administration of statins and accumulation of sitaxentan.

- Dose proportionality and time dependencies

In general pharmacokinetics in healthy volunteers were roughly comparable with patients with PAH. A population pharmacokinetic study revealed that patients had an approximately 30% lower Cl/F compared to healthy subjects. Consecutively, AUC's were significantly higher in patients. This may be due to effect of PAH on hepatic and renal blood flow. The pharmacokinetics of sitaxentan are nonlinear after oral administration to healthy volunteers and subjects with PAH. The AUC and the C_{max} increase more than dose-proportional after increasing oral doses of sitaxentan, while the terminal half life does not change significantly between the different administered doses. Between the dose-interval of 50-100 mg the disproportional increase in exposure is less pronounced. The applicant predicts an approximate 3-fold increase in AUCs between 50 mg and 100 mg. According to the applicant the nonlinear increase in AUC could be due to a more immediate reduction in clearance by inhibition of CYP3A4/5 during the first-pass through the liver. Though less pronounced, dose inproportionality is also found after intravenous administration of sitaxentan. A possible mechanism for this is saturation of the multiple efflux transporters, and as such, the applicant has committed to studying the mechanism of action through use of in vitro and animal models. No unexpected accumulation in the plasma was observed after multiple dosing at the recommended dose of 100 mg once daily. Inter- and intra individual variability for the C_{max} and AUC ranged between the 10 and 35%.

- Special populations

Renal impairment has no influence on the pharmacokinetics of sitaxentan. No information was provided regarding changed pattern of metabolites in urine with renal impairment. No

pharmacokinetic studies were conducted in patients with impaired hepatic function. As the effect of liver impairment on the pharmacokinetics is not clear, and non-linear pharmacokinetics may result in disproportionately higher plasma concentrations of sitaxentan in patients with liver impairment, sitaxentan should not be used in patients with impaired liver function (child-Pugh Class A-C). Gender, race, and age do not clinically significantly affect the pharmacokinetics of sitaxentan. Increasing weight resulted in an increase in apparent clearance. No pharmacokinetic studies with sitaxentan were performed in children.

- Pharmacokinetic interaction studies

In vitro, sitaxentan is a moderately potent inhibitor of CYP2C9 activity and a moderately weak inhibitor of CYP2C8, CYP2C19 and CYP3A4/5 activities. Sitaxentan is a substrate for CYP3A4/5 and CYP2C9.
The $AUC_{0\text{-}inf}$ of S-warfarin (25 mg) increased with sitaxentan administration with 95%, for 100 mg once daily doses of sitaxentan (study FNL02). Also the terminal half-life of warfarin increased after sitaxentan co-administration. Sitaxentan treatment did not influence the C_{max} of S-warfarin. This effect is consistent with the in vitro finding of sitaxentan as CYP2C9 inhibitor. An enhanced effect on prothrombin time and INR also was observed, consistent with the increase in exposure to S-warfarin. Warfarin is not licensed in all EU countries. These results obtained with warfarin can be extrapolated to other anticoagulant drugs used in EU countries for similar indications, as is stated in the SPC. Mean steady state plasma concentrations of ethinyl estradiol and norethindrone (CYP3A4/5 substrate) were higher with concomitant treatment of sitaxentan. The C_{max}, and $AUC_{0\text{-}24}$ of ethinyl estradiol were increased by approximately 35 % and 60 %, respectively. The C_{max} and $AUC_{0\text{-}24}$ of norethindrone were increased by approximately 20 % and 45 %, respectively. Measurements on follicle stimulating hormone (FSH), luteinizing hormone (LH) indicated that there was no effect on anti-ovulatory activity.
No clinical significant interactions on the pharmacokinetics of nifedipine (CYP3A4/5 substrate), sildenafil (CYP3A4/5 substrate), ciclosporin (CYP3A4/5 substrate), digoxin (P-glycoprotein substrate), omeprazole (CYP2C19 substrate), ketoconazole and nelfinavir (CYP2C19 and CYP3A4/5 substrate) were found after concomitant treatment of sitaxentan. The dose of nifedipine used in study FNL04 (3 doses daily of 10 mg) is the minimum advised dose, the maximum advised dose is 6 times 20 mg daily for the immediate release capsules of nifedipine, the maximum advised dose for sustained release tablets of nifedipine is also 120 mg daily. Therefore, in the SPC it is remarked that an interaction with nifedipine with higher doses cannot be excluded.
Concomitant treatment with ciclosporin significantly increased sitaxentan pre-dose levels up to approximately 6-fold. The combination of ciclosporin and sitaxentan is contraindicated in the SPC. The applicant postulates that this interaction may be caused by interaction at the OATB transporter enzyme. The applicant will further investigate this in vitro. If necessary preclinical studies confirm such an interaction in vivo studies will be performed. No clinical significant interactions on the pharmacokinetics of sitaxentan were found after concomitant treatment of ketoconazole (inhibitor of CYP3A4/5) and fluconazole (inhibitor of CYP2C19, CYP2C9, and CYP3A4/5). Regarding the possible impact of polymorphisms of the main metabolizing enzymes (e.g. CYP2C9) it is of relevance that fluconazol (moderate inhibitor of CYP3A4/5, CYP2C9 and CYP2C19) did not significantly change the PK of sitaxentan. Albeit not investigated in subjects with known geno- or phenotype a clinically relevant change in PK in poor metabolizers is therefore unlikely.

Pharmacodynamics

To determine the effects of sitaxentan sodium on cardiovascular haemodynamics and function, studies were conducted in both healthy volunteers and subjects with PAH, left ventricular dysfunction, essential hypertension, and congestive heart failure.

Non-selective blockade of the endothelin receptors has proven to be a useful treatment strategy in primary and scleroderma-associated PAH. It has been postulated that relatively selective antagonism of the ET_A receptor may be further advantageous through blocking the deleterious vasoconstrictive

effects of endothelin-1 (ET-1) on the pulmonary vasculature, while maintaining the vasodilator and clearance functions of the ET_B receptor. To date, the further clinical efficacy anticipated on the basis of this hypothesis remains to be proven. In study TBC11251-220 conducted in patients with hypertension, numerically increased plasma levels of ET-1 were observed after a 2-week oral dosing of sitaxentan 160-480 mg BID, which was statistically significant in the highest dose group (480 mg BID). This supports the endothelin receptor blocking action of sitaxentan with chronic oral administration. It is of note that no pharmacodynamic (PD) studies were conducted in the target population of PAH patients, and that PD studies did not incorporate the 6-Minute Walk Test as a measure of clinical efficacy besides various haemodynamic parameters.

High-dose PD studies were conducted in healthy volunteers and patients with left ventricular dysfunction (LVD). In healthy volunteers, no clinically relevant systemic haemodynamic effects were observed at intravenous (IV) dosages up to 3.0 mg/kg. More relevant PD data came from two studies conducted in patients with LVD. The first study (TBC11251-202, sitaxentan 0.3-10.0 mg/min or placebo IV), showed a dose-dependent reduction in systolic, diastolic and mean pulmonary artery pressure (PAP). Meanwhile, changes in systemic systolic blood pressure, heart rate, cardiac output and cardiac index were generally minor and showed no clear dose-dependency. Systemic diastolic blood pressure showed a moderate dose-dependent reduction. In agreement with these findings, the second study (TBC11251-03, sitaxentan 1.5-6.0 mg/kg or placebo IV) also showed sitaxentan's efficacy in lowering systolic PAP in patients with LVD. The reduction in diastolic PAP observed with sitaxentan was however not significantly different from placebo. Further, a statistically significant reduction in PVR was observed with sitaxentan, indicating a pulmonary vasodilatory response. Overall, these effects, as demonstrated in patients with heart failure, may substantiate sitaxentan's potential therapeutic efficacy in patients with PAH on the basis of a clinically useful effect on PAP and PVR without marked systemic haemodynamic consequences.

The potential clinically useful dose range was difficult to establish from the abovementioned PD studies in the absence of data with multiple oral dosing in the target population of patients with PAH. Instead, the dose selection for the first pivotal clinical study (FPH-01) was mainly based on data from phase II clinical study TBC11251-211 in patients with PAH receiving oral sitaxentan 100-500 mg BID for 12 weeks (see section Clinical Efficacy/Safety). Besides showing favourable effects on relevant PD and clinical efficacy parameters, safety concerns emerged in the extension phase of this study due to clinically significant liver enzyme elevations and hepatitis in 2 subjects; one of these patients died from liver failure (see below). In addition, Michaelis-Menten modelling was conducted using PK data from normal human volunteers. Sitaxentan 100 and 300 mg QD were predicted to yield steady-state trough plasma free-drug concentrations of 1.4-fold and 6.1-fold in excess over the inhibition constant (IC_{50}) value, assuming 99.9% protein binding. Therefore, sitaxentan 100 and 300 mg QD were chosen for study FPH01 in an attempt to reduce risk while maintaining efficacy.

Sitaxentan is an inhibitor of CYP2C9 and, to a lesser extent, of CYP2C19 and CYP3A4/5. The administration of warfarin (S-warfarin is a CYP2C9 substrate) resulted in a larger INR increase in patients pretreated with sitaxentan versus placebo, consistent with sitaxentan's potential to inhibit CYP2C9 and the consequentially increased S-warfarin exposure (AUC) during co-administration. The mean values for the maximum PD effect and area under the PD effect curve were higher with sitaxentan versus placebo. These findings underline the necessity of a dose reduction when sitaxentan is initiated in patients treated with Vitamin K antagonists that are CYP2C9-dependent in their metabolism, to avoid an initially increased bleeding risk. This PD interaction has been taken into account in the phase-3 clinical programme (see section Clinical Safety). No data on dose adaptation in relation to polymorphisms of CYP2C9 have been provided. Consistent with PK findings regarding an increased nifedipine exposure during co-administration with sitaxentan (nifedipine is a CYP3A4/5 substrate), a somewhat increased BP lowering response was observed over time, but the lowest mean SBP and DBP achieved were rather comparable in the sitaxentan 100 mg QD and placebo group, indicating that a nifedipine dose reduction is not necessary. However, the nifedipine dosage selected (10 mg TID) was below the usual maintenance dose, which has been reflected in the SPC. Regarding the sildenafil interaction study (sildenafil is a CYP3A4/5 substrate), the mean maximum positive and

negative changes for both SBP and DBP were rather comparable for the sitaxentan and placebo treatments, indicating no dose-reduction to be necessary in case of co-administration. The anti-ovulatory effect of the oral anticonceptive Ortho-Novum 1/35® was maintained during co-administration. Sitaxentan led to an additional an increase (approximately 2-fold) in plasma concentrations of progesterone in this study. The altered ratio of the oestrogen and the gestagen component may have an impact on the risk/benefit ratio of the oral contraceptive, especially in smoking women, who would have an increased risk for thromboembolism due to the relatively higher (59% increase of ethinyl estradiol versus 47% increase of norethindrone) oestrogen component. This has been reflected in the SPC.

Clinical efficacy

- Dose response studies

Dose finding was based on small initial studies and on investigation of three different doses in the large trials FPH01, 02, and 04.
TBC11251-211 was the initial sitaxentan uncontrolled study to explore efficacy and safety in PAH as a proof of concept study. The study was conducted at doses higher than those used in the subsequent pivotal studies (4-6 mg/kg dosed BID, for total doses of 100-500 mg BID). The study indicated an increase in 6-minutes walk test and of haemodynamic parameters that did not correlate well, however. In the small population of 14 patients, an unfavorable safety profile was shown. Two patients developed acute hepatitis after a total of 4 - 5 months on study drug. One of the patients discontinued the study due to the adverse event (hepatitis), the other one died from liver failure despite reduction and discontinuation of study drug.

Finally, dose finding was established by including 50, 100 and 300 mg QD arms in the large and pivotal clinical trials. As the 50 mg QD dose did not proof to be efficacious and the 300 mg QD dose had an unfavourable safety profile, the pivotal trials revealed 100 mg QD as the therapeutic dose. There does not seem to be a close correlation between plasma sitaxentan levels and clinical efficacy as measured by the 6-minutes walk test. For example, PK data from study FPH-01 suggest that plasma levels are very low after 6h or less with 100 mg QD. There is one PK study comparing 1x200 mg BID vs 2x200 mg QD. It was concluded from that study that if pharmacodynamic outcome is related to Cmax, then the QD regimen may be more appropriate. If, on the other hand, pharmacodynamic outcome is related to overall drug exposure (e.g. AUC), the BID regimen may be more appropriate, because it allows for less fluctuating plasma concentrations, higher CminSS concentrations, and lower CmaxSS concentrations, thus reducing the risk of toxicity while maintaining the necessary plasma concentrations for a pharmacological effect. These mainly theoretical concerns were based on PK data, but were not substantiated by clinical endpoint studies. In study FPH01, the 6-minutes walk test was performed at trough (24h post dosing) at very low plasma levels. Patients with 300 mg had about 48 fold trough plasma levels compared to those on 100 mg, but efficacy was not different. In study FPH02, the 6-minutes walk test was taken at different time points. Furthermore, it took several weeks to achieve a significant therapeutic effect. Overall, these data indicated that the long-term effects on the 6 minutes walk test were not dependent on continuous high plasma levels and can be achieved with a once daily dosing regimen.

- Main studies

The main randomized, double blind, placebo-controlled studies in patients with PAH were **FPH01, FPH02 and FPH04**. Study FPH01 (n=178; sitaxentan 100 or 300 mg, or placebo) was 12 weeks in duration, while FPH02 (n=240; sitaxentan 50 or 100 mg, bosentan, or placebo) and FPH04 (n=98; sitaxentan 50 or 100 mg, or placebo) were 18 weeks in duration.

Table 1: Overview for Controlled Studies: FPH01, FPH02, and FPH04

	FPH01	FPH02	FPH04
Population	Subjects with PAH, 16 to 75 years of age, and NYHA functional Class II, III, or IV	Subjects with PAH, 12-75 years of age, and WHO functional Class II, III, or IV	Subjects with PAH, 12-75 years of age, and WHO functional Class II, III, or IV
Treatment groups	Placebo once daily, sitaxentan 100 mg once daily, sitaxentan 300 mg once daily	Placebo once daily, sitaxentan 50 mg once daily, sitaxentan 100 mg once daily, bosentan *BID*	Placebo once daily, sitaxentan 50 mg once daily, sitaxentan 100 mg once daily
Number of subjects planned	60 per group, total 180	60 per group, total 240	30 per group, total 90
Treatment duration	12 weeks	18 weeks	18 weeks
Number of sites and countries	23 sites in the United States and Canada	55 sites in North America, Europe, Israel, and Australia	11 sites in Mexico, Argentina, Brazil, Spain, and Poland

BID = twice daily; NYHA = New York Heart Association; WHO = World Health Organization

The primary efficacy endpoint in FPH01 was the change from baseline to Week 12 in percent of predicted peak oxygen uptake (VO_2), which is an endpoint of uncertain clinical relevance. The study report did not mention a closed hierarchical stepwise testing procedure, thereby limiting any potential claims on the basis of secondary endpoints, which included the 6-Minute Walk Test as well in FPH01. The primary efficacy endpoint in FPH02 and FPH04 was the change from baseline to Week 18 in the 6-Minute Walk Test distance. Thus, these pivotal studies were not designed to evaluate long-term effects of sitaxentan or to demonstrate improved survival.

The inclusion and exclusion criteria only permitted patients with primary, CTD-associated, or CHD-associated PAH to be enrolled. Consistent with the accepted definition of PAH, a precapillary pulmonary hypertension (mean PAP >25 mmHg at rest) with a PCWP <15 mmHg was required. It is of note that patients with pre-existent hepatic disease were excluded from these studies. No requirement for a 6-Minute Walk Test distance at baseline was postulated for FPH01, but a baseline distance between 150-450 meters was required for FPH02 and FPH04. Complementary to the upper limit postulated for the baseline walking distance, patients with WHO functional class I were excluded. Patients receiving non-conventional PAH treatments (e.g. bosentan, iloprost, sildenafil) were excluded.

Across the pooled ITT population for these studies, a large majority of patients had primary PAH (299/521; 58%) or CTD-associated PAH (129/512; 25%). Most patients were assessed as having WHO functional class II (210/512; 41%) or class III (291/512; 57%), while very few patients were in class IV (11/512; 2%). By exclusion, zero patients were in class I disease severity. Study FPH01 and FPH02 recruited predominantly class III patients, while in FPH04 a majority had a lesser disease severity (class II). As expected, there was a female-to-male preponderance with 80% being female. Studies FPH01 and FPH02 included mostly Caucasians, while in study FPH04 the majority of patients were non-Caucasians (mainly Hispanics or Latinos). Overall, baseline characteristics regarding age, gender, race, PAH aetiology, concomitant medications, and WHO classification were reasonably comparable across treatment groups within each study.

Add-on studies with non-conventional treatments (e.g. sildenafil, iloprost) have not been performed during the clinical development and will be done as part of the post-authorisation commitments (i.e. sitaxentan/sildenafil).

METHODS

Study Participants

All study subjects had documented PAH classified by one of the following: Primary pulmonary hypertension, Secondary pulmonary hypertension related to a connective tissue disease or PAH

associated with congenital heart defects. Additionally they had NYHA/WHO Class II, III or IV symptoms, despite optimal therapy.
Among the exclusion criteria were having parenchymal lung disease, portal hypertension or chronic liver disease.

Treatments
Patients were randomized to the following treatments:
FPH01: 1:1:1 ratio: sitaxentan 100 mg once daily, 300 mg once daily, or placebo once daily, for 12 weeks.
FPH02: 1:1:1:1 ratio: double-blind sitaxentan sodium 50 mg, sitaxentan sodium 100 mg, or placebo once daily; or open-label, rater-blinded, bosentan for 18 weeks. Bosentan was given at the standard dose according to the Package Insert (62.5 mg twice daily [*BID*] for 4 weeks, then increasing to the maintenance dose of 125 mg *BID*)
FPH04: 1:1:1 ratio: double-blind sitaxentan sodium 50 mg plus conventional treatment, sitaxentan sodium 100 mg plus conventional treatment, or placebo plus conventional treatment for 18 weeks. Study drug was taken once daily.

Objectives
The primary objective of the three studies was to evaluate the safety and efficacy of sitaxentan as follows:
FPH01: sitaxentan sodium compared to placebo in patients with PAH.
FPH02: sitaxentan sodium compared to placebo. For descriptive comparison, an open-label bosentan arm was included.
FPH04: sitaxentan sodium compared to placebo.

In these studies, the study medicine was added to patients' current conventional therapy, which could have included a combination of digoxin, anticoagulants, diuretics, oxygen, and vasodilators (e.g., calcium channel blockers, ACE inhibitors). In all three studies the secondary objective was to evaluate the pharmacokinetics of sitaxentan sodium treatment.

Outcomes/endpoints
- Primary efficacy endpoints

FPH01: maximal aerobic capacity defined by change in percent of predicted peak VO_2 from baseline to Week 12 as measured during cycle ergometry. Percent of predicted peak VO_2 was defined as observed peak VO2 divided by the predicted peak VO_2 (based on weight, height, age, and gender) multiplied by 100.
FPH02 and **FPH04:** change from baseline in 6-minute walk distance at Week 18.

- Secondary efficacy endpoints

FPH01:
- 6-minute walk distance changes from baseline to Weeks 6 and 12.
- Shifts from baseline to Week 12 in NYHA functional class.
- Cardiopulmonary haemodynamic changes from baseline to Week 12.
- Anaerobic threshold change from baseline to Week 12 as measured during cycle ergometry.
- Minute ventilation per carbon dioxide production at the AT change from baseline to Week 12 as measured during cycle ergometry.
- Time to clinical worsening (occurrence of either death, epoprostenol use, atrial septostomy, or need for lung transplantation) between baseline and Week 12.
- Time to NYHA functional class deterioration between baseline and Week 12.
- Cycle ergometry exercise time: change from baseline to Week 12.

Other efficacy endpoints:
Quality of life defined by Medical Outcomes Study Short Form 36 (SF-36) questionnaire (Version 2) score change from baseline to Week 12

FPH02:
- World Health Organization functional class change from baseline at Week 18.
- Time to clinical worsening through Week 18. Clinical worsening was defined as any of the following: Hospitalization for worsening PAH, Death, Need for heart-lung or lung transplant, Atrial septostomy, Addition of any new type of chronic treatment for worsening PAH (calcium channel blocker, digitalis, prostacyclin or prostacyclin analog, alternative ET receptor antagonist, phosphodiesterase inhibitor, oxygen), Combined WHO functional class deterioration *and* ≥ 15% decrease in 6 minute walk distance from baseline.
- Borg Dyspnea Score change from baseline at Week 18. The Borg Dyspnea Score assessment was administered at the end of the 6-minute walk test to assess the greatest degree of dyspnea that occurred at any time during the 6-minute walk test. If a subject was not able to perform the 6-minute walk test due to clinical worsening or death, the worst Borg Dyspnea score of 10 was assigned for the visit. During a post-baseline visit, if a subject performed the 6 minute walk test with the addition or increase in the level of oxygen compared to baseline, the worst value of Borg Dyspnea score amongst all values for the individual subject, including the values obtained under oxygen, was assigned.

FPH04:
- World Health Organization functional class change from baseline at each follow up assessment.
- Time to clinical worsening through Week 18 (for definition: see FPH02)

Other efficacy endpoints:
- Borg Dyspnea Score (for definition: see FPH02).

Sample size

In FPH01, a sample size of approximately 180 subjects (60 subjects/treatment group) was estimated to provide approximately 80% power to detect a 4% absolute difference at Week 12 in percent of predicted peak VO_2, as measured during cycle ergometry in at least 1 of the sitaxentan groups compared with placebo. Assuming that (a) the baseline value for sitaxentan-treated subjects for peak VO_2 is 37.2%, and (b) no improvement is observed in placebo subjects through Week 12, a 4% absolute difference in peak VO_2 was necessary to obtain approximately 10% relative improvement, which is considered clinically meaningful. This sample size was calculated based on a type I error of 0.01, equal variance for placebo-treated and sitaxentan-treated groups (SD of 5.4%), 2-sided test, and adjusted for multiple comparisons using the Dunnett test.

Based on results from FPH01, FPH02 had a sample size of approximately 60 subjects per treatment group to detect statistically significant differences between the treatment groups, with 90% overall power at the significance level of 0.05 using a 2-sided Student t test. This study was powered to identify statistical differences in efficacy between the 100 mg sitaxentan and placebo groups. A total of 240 subjects were required to be randomized and treated.

Also based on results from FPH01, FPH04 had a sample size of approximately 30 subjects per treatment group to detect statistically significant difference between treatment group sitaxentan 100 mg and placebo in the primary efficacy endpoint. This estimation was based on a 2-sided student t-test with type I error of 0.05 and statistical power of 85%.

Randomisation

In FPH01, randomization was done assigning the subject the next available blinded drug kit. The blinded drug kit was numbered sequentially according to the randomization schedule, which was stratified by sites and blocked to ensure balance between treatment groups.

In FPH02 and FPH04 an Interactive Voice Response System (IVRS) was used, assigning a drug kit number, blinding the site personnel and the subject to the actual treatment assignment. The bosentan treatment arm in FPH02 was unblinded both for subject and Investigator.

Blinding (masking)

The studies were adequately blinded. Site personnel conducting efficacy assessments were to be conducted by trained personnel who were blinded to the subject's treatment assignment, including coagulation test results and bosentan where applicable.

RESULTS

Participant flow and Recruitment

The disposition of patients and demographic characteristics is presented in table 2 and 3

Table 2: Subject Disposition in FPH01, FPH02, and FPH04

Subject Disposition	Placebo	Sitaxentan 50 mg	Sitaxentan 100 mg	Sitaxentan 300 mg	Bosentan
FPH01					
Randomized and took study drug	60	NA	55	63	NA
Completed study	55 (92%)		55 (100%)	56 (89%)	
Discontinued	5 (8%)		0 (0%)	7 (11%)	
Primary reason for discontinuation					
AE	3 (5%)		0 (0%)	6 (10%)	
Lost to follow-up	1 (2%)		0 (0%)	0 (0%)	
Elevation of LFT values	1 (2%)		0 (0%)	1 (2%)	
ITT Population	60 (100%)		55 (100%)	63 (100%)	
FPH02					
Randomized	62	61	62	NA	62
Took study drug	62	62	61		61
Completed study	51 (82%)	54 (87%)	57 (93%)		52 (85%)
Discontinued	11 (18%)	8 (13%)	4 (7%)		9 (15%)
Primary reason for discontinuation					
Elevation of LFT values > 3 × ULN	1 (2%)	0	1 (2%)		1 (2%)
WHO functional class deterioration + ≥ 15% 6-minute walk distance ↓	2 (3%)	1 (2%)	0		1 (2%)
Need for additional treatment	4 (6%)	3 (5%)	2 (3%)		4 (7%)
AE	1 (2%)	1 (2%)	0		2 (3%)
Subject/Investigator/Sponsor decision	3 (5%)	2 (3%)	1 (2%)		0
Other	0	1 (2%)	0		1 (2%)
ITT Population	61 (98%)	60 (98%)	60 (97%)		59 (97%)
FPH04					
Randomized and took study drug	34	32	32	NA	NA
Completed study	30 (88%)	28 (88%)	29 (91%)		
Discontinued study early	4 (12%)	4 (12%)	3 (9%)		
Primary reason for discontinuation					
WHO functional class deterioration + ≥ 15% 6-minute walk distance ↓	2 (6%)	1 (3%)	0		
Investigator/Subject decision	2 (6%)	2 (6%)	1 (3%)		
Elevation of LFT values > 5 × ULN	0	1 (3%)	1 (3%)		
Pregnancy	0	0	1 (3%)		
ITT Population	34 (100%)	32 (100%)	32 (100%)		

LFT = liver function test; NA = not applicable; ULN = upper limit of the normal range

A large majority of patients completed the pivotal studies in the placebo and sitaxentan treatment groups in FPH01 and FPH04. This was also observed in the sitaxentan, placebo and bosentan treatment groups in FPH02. At least 97% of patients were included in the primary ITT analyses, which is acceptable. Discontinuations will be further discussed in the section on Clinical Safety.

CONDUCT OF THE STUDY

Baseline data

Baseline characteristics can be found in the table below:

Table 3: Demographic Characteristics in FPH01, FPH02, and FPH04

Demographic Characteristics	Placebo	Sitaxentan			Bosentan
		50 mg	100 mg	300 mg	
FPH01	**(N=60)**	**(N=0)**	**(N=55)**	**(N=63)**	**(N=0)**
Mean (SD) age (years)	48 (14.0)		45 (14.1)	44 (11.5)	
Gender					
Male	13 (22%)		8 (15%)	16 (25%)	
Female	47 (78%)		47 (85%)	47 (75%)	
Race or ethnicity					
Caucasian	42 (70%)		39 (71%)	44 (70%)	
Non-Caucasian	18 (30%)		16 (29%)	19 (30%)	
PAH classification					
PPH	37 (62%)		23 (42%)	34 (54%)	
SPH	23 (38%)		32 (58%)	29 (46%)	
CTD	9 (15%)		16 (29%)	17 (27%)	
CHD	14 (23%)		16 (29%)	12 (19%)	
WHO functional class					
Class II	22 (37%)		16 (29%)	21 (33%)	
Class III	36 (60%)		39 (71%)	42 (67%)	
Class IV	2 (3%)		0	0	
FPH02	**(N=61)**	**(N=60)**	**(N=60)**	**(N=0)**	**(N=59)**
Mean (SD) age (years)	53.0 (15.15)	56.8 (13.14)	54.7 (13.75)		48.8 (15.89)
Gender					
Male	15 (25%)	9 (15%)	16 (27%)		13 (22%)
Female	46 (75%)	51 (85%)	44 (73%)		46 (78%)
Race or ethnicity					
Caucasian	45 (74%)	46 (77%)	51 (85%)		47 (80%)
Non-Caucasian	16 (26%)	14 (23%)	9 (15%)		12 (20%)
PAH classification					
PPH	37 (61%)	33 (55%)	38 (63%)		34 (58%)
SPH	24 (39%)[a]	27 (45%)	22 (37%)		25 (42%)
CTD	16 (26%)	19 (32%)	18 (30%)		19 (32%)
CHD	7 (11%)	8 (13%)	4 (7%)		6 (10%)
WHO functional class					
Class II	23 (38%)	20 (33%)	26 (43%)		22 (37%)
Class III	34 (56%)	37 (62%)	33 (55%)		36 (61%)
Class IV	4 (7%)	3 (5%)	1 (2%)		1 (2%)

Numbers analysed

In these studies, a large majority of patients had primary or CTD-associated PAH. Only FPH01 recruited a substantial proportion of patients with CHD-associated PAH, but any claims solely on the basis of this study proved difficult on the basis of the adjudication of endpoints and statistical analysis plan.

Outcomes and estimation

Results on the 6-Minute Walk Test distance (primary endpoint in FPH02 and FPH04)

Table 4. Change from baseline in 6-Minute Walk Test distance (FPH01, FPH02 and FPH04)

6-Minute Walk Distance	Placebo	Sitaxentan			Bosentan
		50 mg	100 mg	300 mg	
FPH01	**(N=60)**	**(N=0)**	**(N=55)**	**(N=63)**	**(N=0)**
Baseline	412.9	NA	394.2	387.1	NA
Mean (SD) change to Wk 6	-0.17 (52.74)	NA	12.71 (55.05)	14.97 (56.64)	NA
95% CI [a]			-11.4, 33.70	-9.12, 34.58	
P-value [b]			0.440	0.327	
Mean (SD) change to Wk 12	-13.44 (62.76)	NA	21.63 (47.57)	19.81 (67.82)	NA
95% CI [a]			8.53, 58.60	6.92, 55.43	
P-value [b]			0.006*	0.009*	
FPH02	**(N=61)**	**(N=60)**	**(N=60)**	**(N=0)**	**(N=59)**
Baseline	322.0	327.4	361.7		335.6
Mean (SD) change to Wk 6	12.55 (52.14)	9.10 (46.92)	18.03 (40.83)	NA	12.48 (61.21)
95% CI		-21.32, 14.41	-11.40, 22.36		-10.60, 30.46
P-value [c]		0.7698	0.6984		0.3337
Mean (SD) change to Wk 12	0.47 (79.14)	5.69 (58.35)	22.89 (59.44)	NA	28.47 (70.78)
95% CI		-19.84, 30.28	-2.80, 47.65		0.83, 55.17
P-value [c]		0.6089	0.0201*		0.0183*
Mean (SD) change to Wk 18	-6.49 (84.37)	17.76 (58.27)	24.91 (57.50)	NA	23.02 (76.41)
95% CI		-1.90, 50.39	3.37, 57.44		0.38, 58.64
P-value [c]		0.0703	0.0316*		0.0526
FPH04	**(N=34)**	**(N=32)**	**(N=32)**	**(N=0)**	**(N=0)**
Baseline	341.6	355.2	342.8		
Mean (SD) change to Wk 6	32.46 (66.91)	27.81 (46.86)	40.71 (53.50)	NA	NA
95% CI		-33.14, 24.01	-21.66, 38.16		
P-value [d]		0.7506	0.5834		
Mean (SD) change to Wk 12	35.12 (71.79)	31.25 (54.85)	51.63 (61.62)	NA	NA
95% CI		-35.43, 27.69	-16.49, 49.50		
P-value [d]		0.8074	0.3214		
Mean (SD) change to Wk 18	31.76 (88.51)	22.18 (48.64)	58.04 (63.65)	NA	NA
95% CI		-47.00, 23.86	-13.84, 62.40		
P-value [d]		0.5163	0.2078		

* Statistically significant difference ($p \leq 0.05$) compared to placebo. Wk: Week, SD: standard deviation.
[a] Simultaneous (Dunnett-Hsu) two-sided CIs (for active versus placebo differences).
[b] Pairwise (versus placebo) p-value was from an analysis of covariance (ANCOVA) including baseline response in the model and adjusted for multiple comparisons using the Dunnett-Hsu method.
[c] P-value was obtained from a nonparametric ANCOVA with the factor of treatment and baseline value as the covariate based on Last observation carried forward (LOCF) imputed data.
[d] P-value was calculated for the comparison with placebo from a 2-sample t-test. Missing values were imputed: LOCF.

Results on study **FPH02** are considered of main importance, since this study included a sufficient amount of patients per treatment group (n=60), adjucated the 6-Minute Walk Test as a primary endpoint, and incorporated a bosentan active-control arm as well. The improvement in 6-Minute Walk Test distance showed some dose dependency in this study, and a statistically significant moderate improvement from baseline in 6-Minute Walk Test distance was noted with sitaxentan 100 mg QD of 24.9 meters versus -6.5 meters with placebo (difference vs. placebo: 31.4 m). Importantly, the bosentan group that was included for descriptive purpose (i.e., without the power to test a hypothesis of non-inferiority), showed a comparable improvement of 23.0 meters after 18 weeks of treatment (difference vs. placebo: 29.5 m).

The results were generally confirmed in study **FPH01** also conducted in a predominantly Caucasian WHO functional class III primary and CTD-associated PAH population, showing a comparable placebo-corrected improvement with sitaxentan 100 mg QD at 12 weeks (35.1 m). The efficacy of sitaxentan 300 mg QD did not improve compared to 100 mg QD in FPH01. Sitaxentan 50 mg QD, that produced statistically insignificant improvements versus placebo at all time points in FPH02, was less efficacious. The results on the change from baseline to Week 12 in percent of predicted peak oxygen uptake were not consistent with the relative improvements in 6-Minute Walk Test distance on sitaxentan, underlining the questionable validity of this alternative primary endpoint in FPH01 reflecting maximal aerobic capacity.

The third pivotal study, **FPH04**, was conducted in a different population of non-Caucasian patients with a lesser disease severity and half as much patients per treatment group (n=32). Large, positive placebo and sitaxentan 100 mg QD treatment effects were noted (33.8 and 58.0 m, resp) compared to the other studies. This may seem remarkable, given the lesser disease severity in FPH04 (i.e., WHO class II instead of class III patients), in which a smaller treatment effect might be expected a-priori in PAH patients. These findings may however relate to sample size and the fact that randomised clinical studies are generally appropriate for comparing treatment effects across randomised treatment groups, while being less suitable for determining the true treatment effect within a given treatment arm. In this respect, it is noted that a smaller relative improvement versus placebo was noted with sitaxentan 100 mg QD in FPH04 (24.2 m) compared to FPH01 and FPH02, consistent with the abovementioned assumption of disease severity-related efficacy. Further, study FPH01 and FPH02 conducted in patients with similar disease severity (class III) showed a good consistency in their relative improvements on sitaxentan 100 mg QD vs. placebo (31.4 and 35.1 m, resp).

In order to allow for an assessment of a potential influence of differences in the concomitant medications between treatment groups, the Applicant presented an overview of classes of medications used by treatment group for pivotal studies FPH01, FPH02 and FPH04, with emphasis on PAH-related and vasodilatory medicinal products. The percentage usages of drugs approved for the treatment of PAH and other vasodilatory medicinal products across the 3 treatment groups in the placebo-controlled trials were not considered sufficiently different in each case to account for differences in efficacy responses between placebo and active drugs (sitaxentan sodium and bosentan). Overall, the relative improvement in exercise capacity (6-Minute Walk Test distance) with sitaxentan 100 mg QD versus placebo (~33 m) appears to be clinically relevant, in view of a numerically comparable relative improvement observed with the previously licensed medicinal product bosentan (30 m). As expected in a rare disease, non-inferiority has not been formally demonstrated. The placebo-corrected improvement in the subgroup of patients dominated by WHO class III patients was 46 m.

The results on the predicted peak oxygen uptake (primary endpoint FPH01) showed statistically insignificant absolute decrease in mean percent of predicted peak VO_2 (i.e., peak exercise oxygen consumption; maximal aerobic capacity) of 0.4% with sitaxentan 100 mg QD compared with a mean decrease of 0.1% in the placebo group. In contrast, sitaxentan 300 mg QD showed a statistically significant absolute increase in mean percent of predicted peak VO_2 of 3.0-4.1%. These results on cardiopulmonary exercise testing are not consistent with the relative improvements with sitaxentan 100 and 300 mg QD regarding the established clinically relevant endpoint of 6-Minute Walk Test distance, which may be due to the fact that both tests measure different abilities. Cardiopulmonary exercise testing is symptom-limited and measures maximal exercise performance, while the 6-Minute Walk Test is time-limited and measures exercise capacity performed at the patient's own pace. In any case, the disparity in outcomes underlines the questionable validity of this alternative primary endpoint in FPH01.

Results on secondary endpoints

In the absence of a pre-specified statistical procedure accounting for multiplicity, the secondary endpoint results for change from baseline in WHO/NYCA Functional Class, Clinical Worsening and Borg Dyspnea Score are considered supportive, and thus not compelling enough to substantiate any specific claims. Sitaxentan 100 mg QD treatment was generally associated with better WHO classification outcome versus placebo at the end of the studies. This was confirmed by the results regarding the incidence of clinical worsening, showing a lower incidence with sitaxentan 100 mg QD

versus placebo in all three studies. Sitaxentan 100 mg QD however failed to produce statistically significantly lower Borg Dyspnoea Scores compared to placebo at the end of the study in FPH02 and FPH04, which also applied for bosentan in FPH02.

Ancillary analyses
Compared to placebo, both sitaxentan 100 and 300 mg QD resulted in statistically significant reductions in PVR and SVR, while a significant increase in cardiac index was noted. For the majority of haemodynamic measurements, only the changes observed with sitaxentan 300 mg QD achieved statistical significance versus placebo (in particular MPAP and MRAP), although a favourable trend towards a decreased MPAP was noted with sitaxentan 100 mg QD.
The maximal exercise performance test revealed no significant differences between sitaxentan treatment groups and placebo in change from baseline to Week 12 in percent of predicted VO_2 at the AT, VE/VCO_2 at the AT, or cycle ergometry exercise time. This latter statistically insignificant result on cycle ergometry time versus a statistically significant improvement on the 6-Minute Walk Test distance required further discussion. Although in a different setting (symptom limited maximal exercise performance vs. time limited exercise capacity at the patient's own pace), both tests intend to measure exercise capacity. This issue was studied and the conclusion was that the exact reason for failure of the cycle ergometry in FPH01 still remained unclear. However, it was agreed that the 6 Minutes Walk Test measuring exercise capacity at the patient's own pace represents the best-validated endpoint in PAH, which was appropriately performed at trough. The change from baseline to Week 12 in heart rate, mixed venous oxygen saturation and systemic arterial oxygen saturation did not differ significantly for either sitaxentan dose group compared to placebo.
Overall, sitaxentan 100 mg QD may be considered as having a moderately favourable effect on pulmonary vascular haemodynamics in patients with PAH on the basis of its PAP and PVR lowering potency, without affecting oxygenation status. These findings are in line with previous findings in pharmacodynamic studies in patients with LV dysfunction (see section on Clinical Pharmacology).

- Supportive studies

<u>Supportive efficacy: studies FPH01-X, FPH02-X and FPH03</u>
These long-term studies were primarily safety studies. Efficacy results on these studies should be cautiously interpreted due to the lack of a placebo or active control arm (except for FPH02-X that included a bosentan treatment arm) and their open-label nature (except for FPH01-X that was blinded to treatment).
The large open-label study **FPH03** (sitaxentan 100 mg QD) that produced interim data on a substantial amount of patients up to Week 28 (n=229), suggested moderate improvements in exercise capacity and WHO functional classification, but no effect on Borg Dyspnoea Score with sitaxentan 100 mg QD up to this time point. These results are in line with previous findings from the pivotal trials up to 18 weeks' duration.
Study **FPH02-X** (sitaxentan 100 mg QD or bosentan) produced interim data on a substantial amount of patients up to Week 18 (n=98) and suggested some further improvement of exercise capacity from preceding study FPH02 in both the sitaxentan and bosentan group. This was likely related to the fact that placebo and sitaxentan 50 mg QD-treated patients were switched to either sitaxentan 100 mg QD or bosentan in the extension phase.
In study **FPH01-X** (n=170), 5% of patients receiving sitaxentan 100 mg QD experienced a deterioration of NYHA functional class over a mean exposure of 29 weeks compared to 0% on sitaxentan 100 mg QD and 7% on placebo within the 12 weeks of the preceding pivotal FPH01 study, which is acceptable. Overall, within the limitations posed by the absence of a placebo or active control arm and the open-label nature, these studies suggested maintenance of sitaxentan's efficacy up to 28 weeks of treatment.

<u>Patients failing on bosentan treatment: study FPH06</u>
FPH06 (n=48) was a randomized, double-blind, 12-week study with 50 or 100 mg QD sitaxentan given orally to patients with PAH who had failed bosentan therapy either due to lack of clinical response or due to safety concerns/dose-limiting toxicity. In principle, the administration of sitaxentan

in patients who have failed on bosentan (a drug with a similar mechanism of action) has a questionable clinical rationale. The interpretation of the results of this small-sized study was not straightforward in the absence of a placebo or active control arm, although ethical (placebo) and practical (unavailability of commercial bosentan to allow blinding) difficulties were acknowledged. The subset of patients who entered the study on the basis of safety reasons (n=13) was too small to allow for any meaningful conclusion in this context. In the 'lack-of-efficacy' subset (n=35), 7 (20%) and 6 (17%) sitaxentan-treated patients respectively showed an in- and decreased 6-Minute Walk Test distance of at least 15% at Week 12. In this same subset, 2 (6%) and 6 (17%) respectively showed an improvement and progression (i.e., deterioration) in WHO functional classification. In the context of the aforementioned methodological limitations, these results were not considered compelling enough to support any specific recommendation in patients experiencing a lack of efficacy on bosentan.

Clinical safety

Sample size allowed only common AEs to be analysed in subgroups; no subgroup data on SAE and discontinuations were provided.

- Patient exposure

Across all phase 2 and 3 studies in patients with PAH, 899 patients have been treated with sitaxentan with a mean exposure of 29 weeks, while 155 and 83 patients have been exposed to placebo or bosentan for mean duration of 15 and 27 weeks, resp. Of the 526 sitaxentan patients exposed for at least 6 months, 378 (72%) have been treated ≤ 12 months, 136 (26%) have been treated for at least 1 year but < 1.5 years, but very few patients received sitaxentan past 1.5 years (12 patients). Of the 48 patients in the bosentan group exposed for at least 6 months, 41 (85%) have been treated ≤ 12 months, while only 7 patients (15%) have been treated for at least 1 year.

- Adverse events

In the medium-term phase 3 placebo-controlled studies in patients with PAH, at least 1 treatment emergent AE was experienced by comparably high proportions among treatment groups (all sitaxentan 91%, sitaxentan 100 mg QD 92%, placebo 92%, bosentan 89%). AEs that occurred in more than 10% of sitaxentan 100 mg QD patients included headache (28%), oedema peripheral (21%), nausea (15%), upper respiratory tract infection (15%), dizziness (13%), nasopharyngitis (13%), nasal congestion (13%) and insomnia (13%). The incidences of specific AEs were comparable between sitaxentan and placebo treated patients, except for marked higher incidences (difference ≥ 5%) on peripheral oedema (21% vs. 16%), insomnia (13% vs. 6%), nasopharyngitis (13% vs. 7%), nasal congestion (13% vs. 6%), upper respiratory tract infection (15% vs. 8%) and epistaxis (8% vs. 3%) with sitaxentan 100 mg QD versus placebo. However, when the preferred terms of oedema and peripheral oedema were combined, the overall incidence was comparable between the sitaxentan 100 mg QD (22%), placebo (21%) and bosentan (23%) group. When nasopharyngitis, nasal congestion, sinus congestion, sinusitis, upper respiratory tract infection and pharyngolaryngeal pain were combined, the overall incidences were higher in the sitaxentan 100 mg QD and bosentan groups (45% and 48%, resp) compared to the placebo group (32%). Marked incidence differences (difference ≥ 5%) in the sitaxentan 100 mg QD versus bosentan group concerned vomiting (5% vs. 0%, resp), muscle cramp (7% vs. 0%), headache (28% vs. 20%), insomnia (13% vs. 0%), cough (5% vs. 13%), dyspnoea (7% vs. 15%) and pulmonary hypertension (1% vs. 7%). The increased incidence of epistaxis with sitaxentan may be related to a higher incidence on INR increased (sitaxentan 100 mg QD 6%, placebo 4%, bosentan 3%), for which a sitaxentan dose-dependency was demonstrated (50-300mg; 4%-14%).
Regarding common AEs judged to be drug-related, sitaxentan treatment was associated with higher rates on coagulation/bleeding-associated (INR increased, PT prolonged, epistaxis) and vasodilation-associated (peripheral oedema, flushing) AEs compared to placebo. The presence of a dose-dependency further supports the association with study drug for these AEs. Overall, sitaxentan and bosentan were generally associated with higher rates on upper respiratory tract disorders and vasodilation-associated events (mainly peripheral oedema) compared to placebo, while sitaxentan further elicited an increased rate on bleeding events (mainly epistaxis).

Adverse events were also analysed by subgroup. Females treated with sitaxentan 100 mg QD experienced peripheral oedema more frequently compared to males, while no such difference was observed in placebo-treated female and male patients. However, no consistent difference was noted in AE frequencies between female and male sitaxentan-treated patients. Sitaxentan's safety profile appeared to be more favourable in Caucasians on the basis of lower frequencies for most AEs in Caucasian versus non-Caucasian patients (i.e., Latinos and Hispanics). Within the limitations posed by the low number of elderly patients (≥65 years) treated with either sitaxentan or placebo (n=27 and 24, resp), no consistent difference was noted in AE frequencies between patient's aged 18-65 and the elderly. Sitaxentan's AE profile appeared to be comparable in patients with primary and CTD-associated PAH, as well as in patients in WHO functional class II versus III.

- Serious adverse event/deaths/other significant events

In the phase 2 and 3 oral studies conducted in patients with PAH, at least 1 SAE was experienced by comparable proportions of patients across treatment groups; sitaxentan 23%, placebo 20%, bosentan 25%. A lower proportion of PAH patients experienced serious cardiac disorders (predominantly right ventricular failure, chest pain and cardiac failure) in the all doses sitaxentan compared to the placebo group (5.3% vs. 7.1%, resp), but this rate was lowest in the bosentan group (3.6%). On the other hand, serious respiratory disorders (predominantly pulmonary hypertension, pneumonia and dyspnoea) were less frequently observed in the all doses sitaxentan group compared bosentan (9.1% vs. 14.5%, resp), while this proportion was lowest in the placebo group (3.2%). An increased INR was more frequently reported as SAE with sitaxentan compared to all other groups, but the overall absolute incidence was low in the sitaxentan 50-100 mg QD group (0.4%). Notably, the incidence of anaemia reported as SAE was lower with sitaxentan and bosentan compared to placebo (≤ 0.4% vs 1.3%, resp). When combining the SAEs hepatic enzyme increased, liver function test abnormal, ALT increased and AST increased, the incidences with sitaxentan 50-100 mg QD and bosentan were comparable (1.0% and 1.2%, resp) and higher than placebo (0.6%). Overall, the SAE profile of sitaxentan 100 mg QD appears to be comparable to bosentan, although the small number of patients in this latter treatment group (n=83) precludes drawing robust conclusions in particular regarding relatively infrequently occurring SAEs such as hepatitis (see below).
The incidence of death in the medium-term pivotal studies FPH01, FPH02 and FPH04 was lower with sitaxentan compared to placebo (1/306=0.3% sitaxentan; 2/155=1.3% placebo), while no deaths occurred in the smaller group of patients treated with bosentan (n=61). As expected, most deaths were due to cardiopulmonary causes. In general, the poor prognosis of the disease, the limited amount of patients treated and the lack of a control group make it difficult to draw conclusions about the causality of deaths in the long-term extension studies. The only long-term study incorporating a control arm for descriptive purpose was FPH02-X, in which 5/125=4.0% sitaxentan-treated and 3/65=4.6% bosentan-treated patients died from various causes, thereby posing no safety concerns. One death of particular interest was observed in the preceding phase 2 clinical study TBC11251-211-X (extension phase), in which a patient initially dosed with sitaxentan 300 mg BID died from hepatic failure, indicative of drug-related hepatotoxicity. This death urged the applicant to reduce the target dosage ≤ 300 mg QD in the pivotal phase 3 studies. Notably, no clinical significant interactions on the pharmacokinetics of sitaxentan were found after concomitant administration of CYP3A4/5 or CYP2C9 inhibitors (see PK section). Overall, the incidence of death experienced at the SPC recommended dose level does not raise major safety concerns, but any claim towards the prevention of mortality relative to current standards of medical care remains unjustified in the absence of clinical outcome studies.

- Laboratory findings

<u>Hepatic toxicity</u>
The rates on treatment emergent elevations in ALT values > 5 × ULN in phase 2 and 3 oral studies in PAH patients were 0.7% for placebo, 4% for sitaxentan 100 mg QD, and 6% for bosentan. A comparable pattern was observed when analysing a lower aminotransferase threshold, since the rates of elevations in ALT and/or AST values > 3 × ULN were 5% for placebo, 7% for sitaxentan 100 mg

QD, and 12% for bosentan. In a head-to-head comparison in the randomised active-controlled studies FPH02 and FPH02-X, the Kaplan-Meier risk of elevation in ALT and/or AST values > 3 × ULN within the first year of exposure was less for sitaxentan sodium 100 mg QD (4%) than bosentan (14%). The majority (90%) of elevations in aminotransferases occur by 9 months and typically returned to normal or baseline by 4 months in both usual- and special risk patients. The assessment of safety data regarding hard clinical endpoints such as hepatic failure is restricted by the infrequent nature of these events, the limited amount of PAH patients treated, and the frequent presence of confounding risk factors in these seriously ill patients. A detailed analysis of patients with ALT > 5 × ULN yielded a total of 7 patients on sitaxentan 100 mg QD that met Hy's rule[2] and/or had clinically symptomatic hepatitis. Two of these 7 patients were reported to have clinically symptomatic hepatitis, of which one proceeded to liver failure. Overall, the data suggest that the hepatotoxicity of sitaxentan is at a comparable level versus bosentan, although firm conclusions should not be drawn on the basis of these limited data obtained so far. The SPC contains contra-indications, warnings, and strict monitoring plus stopping rules related to hepatic function. Also, sitaxentan will be distributed using a controlled access system and hepatotoxicity will be monitored in a post-marketing surveillance system. The underlying mechanism of hepatotoxicity remains unclear at present

Haemoglobin reductions

In the current placebo-controlled studies in patients with PAH, the mean change in haemoglobin, hematocrit, RBCs, and WBCs showed a consistent pattern of decreased values at the end of treatment, which was also observed with bosentan. A sitaxentan dose-dependency was noted. The magnitude of the decreases in these parameters was generally comparable in the sitaxentan 100 mg QD and bosentan treatment group (e.g. reduction in haemoglobin; 0.5 vs. 0.7 g/dL, resp). The proportion of patients with decrease in haemoglobin ≥ 1.0 g/dL was substantially larger in the sitaxentan 100 mg QD and bosentan treatment group compared to placebo (~60% vs. 32%, resp), while the proportion of patients with ≥ 15% decrease from baseline resulting in a value less than the lower limit of normal was larger with sitaxentan 100 mg QD compared to placebo and bosentan (7% vs. 3%, resp). A comparable pattern was observed for hematocrit. The proportionally small mean changes in platelets observed with sitaxentan and bosentan were of minor clinical relevance. In patients exposed for at least 6 months, the proportion of patients who experienced at least a 1.0 g/dL decrease from baseline in haemoglobin was comparable in the sitaxentan 100 mg QD and bosentan group (68% vs. 66%, resp). Also, the proportion of patients with ≥ 15% decrease from baseline in haemoglobin resulting in a value less than the lower limit of normal was comparable in the sitaxentan 100 mg QD and bosentan group (8% vs. 9%, resp). Again, a similar pattern was observed regarding hematocrit. The mean reduction in haemoglobin and hematocrit tended to decrease in the course of 12 months.

Overall, complementary to previous data obtained with bosentan, these data indicate that haemoglobin (and hematocrit) reductions are a dose-dependent class effect of ETRAs. The cause for this change remains unclear, although underlying mechanisms related to hemodilution, a slow production effect and slow blood loss have been postulated. Of note, anaemia as SAE was infrequently reported on sitaxentan and bosentan, with a lower rate versus placebo (≤ 0.4% vs. 1.3%, resp).

The SPC on sitaxentan sodium recommends haemoglobin to be measured before initiating treatment and periodically thereafter.

Bleeding events

In patients using warfarin or warfarin analogues, the incidence of bleeding was higher in the all doses and 100 mg QD sitaxentan groups compared to the placebo group (39/225=17% and 15/110=14% vs. 12/117=10%, resp). This bleeding pattern is likely mainly driven by the interaction between sitaxentan and warfarin (increasing the INR), that was not accounted for during the initial part of the clinical phase 3 programme. The lower bleeding rate with bosentan versus placebo (2/41=4.9% vs. 10%, resp) may be secondary to induction of warfarin metabolism by bosentan. Remarkably, no dose-dependency was noted across sitaxentan 50-300 mg/day. Approximately half way through study FPH01, a protocol amendment was made to reduce the warfarin dose at sitaxentan initiation. Very few cases of bleeding

[2] Zimmerman HF. Hepatotoxicity: The adverse effects of drugs and other chemicals on the liver. 2nd Edition. Philadelphia: Lippincott Williams & Wilkins, 1999: 428.

events associated with INR > 3.5 occurred after this amendment in FPH01; zero on placebo, 1 on sitaxentan 100 mg QD (ecchymosis/INR 4.9), and 1 on sitaxentan 300 mg QD (haemoptysis/INR 6). After the protocol amendment, the incidence of INR > 3.5 with sitaxentan 100 mg QD were rather comparable to placebo (3.1% vs 2.1%, resp). The interpretation of these data is hampered by the limited amount of patients treated in this study (n=178), but would suggest that INR was generally adequately controlled taking into account the required warfarin dose-reduction prior to initiating sitaxentan treatment and subsequent INR monitoring according to clinical practice. An initial anticoagulant dose reduction will also be necessary for other Vitamin K antagonists that are CYP2C9 dependent in their metabolism (i.e., acenocoumarol, fenprocoumon and fluindione), which has been reflected in the SPC. Notably, one patient with an INR above 3.5 in the sitaxentan 300 mg group of study FPH01-X did not receive warfarin. The finding was unexplained. In the long-term treatment a significant increase was found only at one visit and a slight increase at the following one. Since there was no obvious drug related rationale, the applicant suggested that the finding was possibly due to a sampling error. A direct effect of sitaxentan on INR is not suggested by this finding.

Semen and male fertility hormone evaluations

In pre-clinical studies conducted in rats, mild focal abnormalities (atrophic seminiferous tubules) were observed in the testes of adult rats. In contrast, studies with beagle dogs revealed no evidence for similar testicular effects as observed in the rat. In view of these findings, semen samples from PAH patients were collected on a voluntary basis during the clinical program. No consistent adverse sitaxentan treatment effects on the total motile sperm count (an indicator for male fertility status) or hormone levels (FSH, inhibin-B, LH, testosterone) were observed, thereby providing no evidence for widespread sitaxentan-induced atrophic tubules in PAH patients. Pre-clinical findings are reflected in section 5.3 of the SPC.

ECG/QT

A thorough QT study in healthy volunteers was performed comparing placebo, sitaxentan 100 and 1000 mg p.o.QD and moxifloxacin 8mg. Neither the uncorrected QT values nor the QTcI and the QTcF values indicated a signal of concern. When applying the Bazett's correction the placebo corrected upper 95% CI limit for Sitaxentan 1000 mg is 11 ms. This is just above the range of 10 ms that has been suggested as a criterion for a negative thorough QT study (ICH E14 CHMP/ICH/2/04) ensuring that a drug prolongs the mean QT/QTc interval by around 5 ms or less. This is not of concern, however, and can be explained by an overcorrection using the Bazett's correction at a higher HR. Similarly, the outlier analysis was unremarkable. Electrocardiogram results from patients with PAH from Study FPH02, including heart rate, PR interval, QRS interval, QT interval, and QTcB interval, were independently evaluated. Overall, the ECG data did not indicate concerns regarding QT. A specific analysis of ECG changes in patients with renal failure did neither indicate a correlation between pharmacokinetics in these patients nor a clinical concern.

- Discontinuation due to adverse events

In the phase 3 placebo-controlled studies in patients with PAH, a large and comparable proportion of patients treated with sitaxentan (92%), placebo (87%) or bosentan (85%) completed the studies. The most common reasons for premature discontinuation in the all doses sitaxentan, sitaxentan 100 mg QD, placebo and bosentan treatment groups were AEs (2%, 0%, 3% and 3%, resp) and need for additional chronic PAH treatment (2%, 1%, 3% and 7%, resp). In the largest safety pool of all phase 2 and 3 oral studies in patients with PAH, the overall AE-associated discontinuation rate was comparable in the sitaxentan >50 to ≤100 mg QD and placebo group (9% and 8%, resp), while being higher in the bosentan group (15%). Discontinuations due to cardiac disorders were infrequent across all treatment groups at rates below 1.2%, but respiratory disorder-associated discontinuations were generally more frequently observed at rates between 3.2%-4.8%. Clinical investigations-related discontinuations (mainly driven by hepatic function test abnormalities) occurred most often in the bosentan group (placebo 1.3%, all doses sitaxentan 3.9%, sitaxentan >50 to ≤100 mg QD 2.8%, bosentan 4.8%). However, in view of small differences in incidences across treatment groups and a

low number of bosentan-treated patients, once again it is noted that these data should be cautiously interpreted.

- Discontinuation of treatment

The potential for any sitaxentan withdrawal events was not formally assessed as part of the phase 3 clinical program. This was due to the fact that these effects are not usually expected with drugs that take several weeks to show efficacy, and due to feedback from Investigators involved in the initial high dose TBC3711-211 study, as well as the FPH01 and bosentan trials. However upon request this point was further analyzed comparing the treatment-emergent AEs reported by the final day of therapy compared to those that occurred 24-72 hours beyond discontinuation. The conclusion was that even though it is impossible to be definitive with respect to a lack of withdrawal effects, the data continue to support the opinion of the Investigators that acute withdrawal effects are not a concern with sitaxentan sodium or this class of drugs.

- Post marketing experience

There has been no post marketing experience to date.

5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Use in Paediatric/adolescent patients	• Routine pharmacovigilance activities. • Additional information from clinical trials	• Contraindication for children and adolescents under 18 years in section 4.3 of the SPC • Educational pack for physicians

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Hepatotoxicity	• Routine pharmacovigilance activities. • Enhanced pharmacovigilance triggered by relevant LLTs • Monitoring using electronic data capture system. • Investigating the effects of sitaxentan sodium on the ABC efflux-transporters (BSEP) and any other transporters, through use of in vitro and animal models. As appropriate, clinical pharmacology studies in healthy volunteers will be performed to further characterize in humans those effects observed in pre-clinical models.	• Contraindication for patients with pre-existing hepatic disease (Child-Pugh Class A-C) and in patients with pre-treatment elevation of liver aminotransferases above 3 x ULN in section 4.3 of SPC. • Monthly monitoring of liver function with physicians requested to provide results via the proposed database. • Advice on treatment changes should aminotransferase levels rise above 3 x ULN but below 5 x ULN is provided in section 4.4 of the SPC. Treatment should be stopped immediately if aminotransferase levels rise above 5 x ULN. • Physicians and patients will receive educational material concerning sitaxentan sodium hepatotoxicity. • The pack size will be limited to 28 tablets.
Anaemia (decreases in haemoglobin and related red cell parameters)	• Routine pharmacovigilance • Enhanced pharmacovigilance triggered by relevant LLTs • Monitoring using electronic data capture system.	• Physicians and patients will receive educational material concerning safety concern. • Haemoglobin concentrations are to be checked prior to treatment, after 1 and 3 months, and every 3 months thereafter. Physicians will be requested to provide results via the proposed database.
Teratogenicity	• Routine pharmacovigilance • Enhanced pharmacovigilance triggered by relevant LLTs • Monitoring using electronic data capture system.	• Physicians and patients will receive educational material concerning safety concern. • The SPC (section 4.6 and 5.3) contains appropriate language concerning teratogenicity. • Treatment should not be initiated unless a woman is practicing reliable contraception. • The pack size will be limited to 28 tablets. • Need for negative pregnancy test prior to prescription.
Potential risk for increased adverse events in non-caucasians	• Routine pharmacovigilance • Enhanced pharmacovigilance triggered by relevant LLTs • Monitoring using electronic data capture system.	

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Pre-existing hepatic disease or pre-treatment elevation of liver aminotransferases	• Routine pharmacovigilance • Monitoring using electronic data capture system.	• Dosage in hepatic impairment is covered in sections 4.2, 4.3 and 4.4 of the SPC (see hepatotoxicity)
Pulmonary oedema / pulmonary veno-occlusive disease	• Routine pharmacovigilance • Monitoring using electronic data capture system.	• Physicians will only be allowed to prescribe sitaxentan sodium after pre-certification training through the controlled access programme. • An appropriate warning will be included in section 4.4 of the SPC concerning the potential for this complication to occur.
Concomitant use of vitamin K antagonists	• Routine pharmacovigilance • Enhanced pharmacovigilance triggered by relevant LLTs • Monitoring using electronic data capture system.	• Physicians will only be allowed to prescribe sitaxentan sodium after pre-certification training through the controlled access programme. • Appropriate guidance on vitamin K dosage adjustment is included in sections 4.4 and 4.5 of the SPC.
Co-administration with OATP Inhibitors	• Routine pharmacovigilance • Enhanced pharmacovigilance triggered by relevant LLTs • Monitoring of concomitant medication using electronic data capture system. • Investigation of a possible link between OATP inhibitors and plasma levels of sitaxentan will be investigated by means of pre-clinical experimentation including *in-vitro* determinations of drug-drug interactions and a clinical study with pravastatin.	• Physicians and patients will receive educational material concerning sitaxentan sodium safety concerns. • Appropriate warnings included in sections 4.4 and 4.5 of the SPC.
Co-administration of ciclosporin A	• Routine pharmacovigilance	• A contraindication is included in sections 4.3 and 4.5 of the SPC.
Usage in combination with sildenafil and prostaglandins	• Routine pharmacovigilance • Enhanced pharmacovigilance triggered by relevant LLTs • Monitoring using electronic data capture system. • Encysive will perform a clinical study on combination therapy with sitaxentan sodium and sildenafil post approval.	• The effect of sitaxentan on sildenafil is included in section 4.5 • Spontaneous reports of adverse events will include recording of concomitant medications to allow the monitoring of safety of the concomitant use of sitaxentan sodium with sildenafil and prostaglandins through analysis of ADRs.

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Phototoxicity	• Photosafety: a copy of the final study report for Study LOG0001: Neutral Red Uptake Phototoxicity Assay of Sitaxentan Sodium (TBC11251Na) in 3T3 Mouse Fibroblasts is due by the end of October 2006.	
Potential for medication error	• Routine pharmacovigilance • Review of ADRs which might suggest medication error	• Use of packaging design, colours and labelling to avoid any possible confusion with another product of a similar name

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

The MAH shall set up a surveillance programme to collect information on: the demographics of patients prescribed Thelin, any adverse reactions and reasons for discontinuation of Thelin. Details of such a surveillance programme should be agreed with the National Competent Authorities in each member state and put in place prior to marketing of the product.

The MAH must agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that, prior to prescribing, all doctors who intend to prescribe Thelin are provided with a physician information pack containing the following:

- Product information
- Physician information about Thelin
- Patient information card
- Partner of patient information card

The physician information about Thelin should contain the following key elements:

- That Thelin is teratogenic
  - Need for pregnancy testing prior to first and subsequent prescriptions
  - Use of effective contraception in women of child bearing age
  - Possible interaction with oral contraceptives and increased risk of thromboembolism
  - Need to advise female patients about teratogenicity, need for pregnancy testing and contraception, what to do if they become pregnant
  - Referral of patients who become pregnant to a physician specialised or experienced in teratology and its diagnosis for evaluation and advice

- That Thelin is hepatotoxic
  - Need for liver function tests prior to and during treatment
  - Contraindication in patients with pre-existing hepatic disease
  - Discontinue sitaxentan sodium immediately if liver enzymes rise above 5 x ULN
  - Need for close monitoring if liver enzymes measure between 3 and 5 x ULN, with discontinuation if a repeat analysis is above 3 x ULN, and not restarted until levels have returned to below 3 x ULN

- That treatment with Thelin often causes a decrease in haemoglobin and related red cell parameters
    - Need for full blood count prior to use and monitoring at clinically appropriate intervals

- That there is an increased risk of bleeding with Thelin
    - Interaction with warfarin and vitamin K antagonists leading to an increased INR
    - Need to decrease established dose of vitamin K antagonist upon starting sitaxentan therapy
    - Start vitamin K antagonists treatment at a reduced dose if already on sitaxentan sodium
    - Need for regular monitoring of INR
    - Co-prescription with sildenafil may increase the risk of haemorrhage
    - Be aware of the potential for haemorrhage and investigate as appropriate

- That there is an interaction with ciclosporin A which may lead to higher blood concentration of Thelin and hence an increased risk of adverse reactions.

- That the safety database of Thelin is limited and physicians are encouraged to enrol patients in a surveillance programme to increase knowledge about the incidence of important adverse drug reactions (ADRs). The surveillance programme should prompt doctors to report serious ADRs and certain selected ADRs as below immediately and other non-serious ADRs at three monthly intervals.

The information collected should include:

- Anonymised patient details – age, sex and aetiology of PAH
- Concomitant medications
- Reason for discontinuation
- ADRs
    - All serious ADRs
    - Increase in hepatic enzymes to > 3 x ULN
    - Anaemia
    - Haemorrhage
    - Pregnancy and outcome
    - Pulmonary oedema
    - Suspected interactions
    - Unexpected ADRs according to the SPC.

The Patient information card should include the following information

- That Thelin is teratogenic
- The need for a negative pregnancy test immediately prior to first prescription
- The need to ensure that women of child bearing age are using effective contraception and that patients should inform their doctors of any possibility of pregnancy before a new prescription is issued
- The need for female patients to contact their treating doctor immediately if they suspect that they might be pregnant.
- That Thelin is hepatotoxic and they will need to attend for regular blood tests
- That Thelin may cause bleeding
- The need to tell their doctor about any adverse events
- The need to tell health care practitioners that they are taking Thelin

Partner of patient information card should include the following information:

- That Thelin is teratogenic and that women of child bearing age must use effective contraception

The Name Review Group has required monitoring of potential medication errors with Teolin, and as such this has been reflected in the Risk Minimisation activities and has been included as a post-authorisation commitment.

6 Overall conclusions, risk/benefit assessment and recommendation

Quality

There are no unresolved quality issues that could have a negative impact on the benefit/risk balance. The quality of the product is satisfactory.

Non-clinical pharmacology and toxicology

Sitaxentan sodium is a highly selective ET_A receptor antagonist that has shown in several animal models to be effective for pulmonary hypertension.
Overall, the primary pharmacodynamic studies provided adequate evidence that sitaxentan is effective for pulmonary hypertension (PAH) in response to hypoxia. The safety pharmacology studies using rats, mice and dogs showed that the effects of sitaxentan on the renal, gastrointestinal and respiratory system in different species had no major side effects.

The data obtained form the general pharmacokinetic point of view give a good picture of sitaxentan kinetics at high doses in several different animal species, however there is no PK data at lower doses i.e. for human application a dose of 100 mg/day. Sitaxentan binds to high degree to plasma proteins, and its metabolites are weak or potent inhibitors of CYP2C9, CYP2C19, and CYP3A4 activity, and possibly of CYP2C8. Sitaxentan may induce enzymes responsible for its own metabolism, and is eliminated via hepatic and renal clearance. Studies on interaction of sitaxentan with the hepatic transporter protein and on the metabolite in fraction P8 are still to be performed as post authorisation commitments to further elucidate the mechanism of action and possible toxicity of sitaxentan.

The results of the toxicology programme revealed that a QD administration was better tolerated than a BID dosing regimen. Dose-related liver changes (weight, centrilobular hypertrophy, occasionally necrosis), induction of hepatic drug metabolising enzymes and slightly decreased erythron parameters were seen in mice, rats and dogs. At high doses, dose-related increases in prothrombin time (PT) and activated partial thromboplastin time (APTT) were also seen, most prominently in rats, and coagulopathy (bleedings) in rats and dogs, but not mice. The significance of these findings for humans is unknown. Genotoxicity studies both in vivo and in vitro did not provide any evidence for a clinically relevant genotoxic potential. Carcinogenicity studies gave negative results when conducted for 97-99 weeks in rats, and for 6 months in $p53^{(+/-)}$ transgenic mice.
Reproductive toxicology was evaluated only in rats where considerable teratogenicity was observed. This was seen at the lowest tested dose, corresponding in rats at exposures more than 30 times the human exposure. Since lower doses have not been tested, it is not clear whether there is a safety margin for human, and if the teratogenic effects observed represent a class effect of endothelin receptor antagonists. Thus far, Bosentan is the only registered ET receptor antagonist. Available preclinical information is insufficient to compare the reproduction toxicity findings of sitaxentan with those of bosentan. There are no data on the use of sitaxentan in pregnant women, but there is a need to treat hypertensive women of child bearing potential, also in situations when other treatment alternatives are not suitable. Following with these data the discussion scheme in the Discussion Paper on Contraindications in Pregnancy, it is concluded that there is no need to contraindicate sitaxentan sodium in pregnancy.

Sitaxentan sodium is not recommended for use in children or adolescents under the age of 18 years. To further investigate its use in the children population, the MAH will perform a paediatric clinical programme as a post-authorisation commitment. The MAH has also agreed to perform a phototoxicity study as part of the post-authorisation commitments in order to evaluate the possibility that the increased number of skin tumours could be related to phototoxicity.

Repeated-dose toxicity studies and the carcinogenicity study did not reveal any concern regarding a possible immunotoxic effect of sitaxentan.

Finally, no ecotoxicity/environmental risk assessment (ERA) has been performed as the current Draft "Note for Guidance on the Environmental Risk Assessment" waives the need for ERA in orphan drugs.

Efficacy

The main randomized, double blind, placebo-controlled studies designed to evaluate safety and efficacy in patients with PAH were FPH01, FPH02 and FPH04. All the patients included in these studies had PAH ranging from NYHA/WHO functional class II to IV, and presented primary, CTD-associated, or CHD-associated PAH. The primary efficacy endpoint in FPH01 was the change from baseline to Week 12 in percent of predicted peak oxygen uptake (VO_2). In the other two pivotal trials the primary efficacy endpoint was the change from baseline to Week 18 in the 6-Minute Walk Test distance. These studies were not designed to evaluate long-term efficacy of sitaxentan or to demonstrate improved survival. At present, combination studies with non-conventional PAH treatments have not been performed, but a clinical study to evaluate the clinical efficacy and safety of sitaxentan and sildenafil (Revatio®) in co-administration is has been committed to as a follow up measure

Results on study FPH02 are considered of main importance, since this study included a sufficient amount of patients per treatment group (n=60), adjucated the 6-Minute Walk Test as a primary endpoint, and incorporated a bosentan active-control arm as well for descriptive purpose. The improvement in 6-Minute Walk Test distance showed dose dependency in this study, and a statistically significant moderate improvement in 6-Minute Walk Test distance was noted with sitaxentan 100 mg QD compared to placebo. The results were generally confirmed in study FPH01 also conducted in a predominantly Caucasian WHO functional class III primary and CTD-associated PAH population, showing a comparable placebo-corrected improvement with sitaxentan 100 mg QD at 12 weeks. The alternative primary endpoint in FPH01 reflecting maximal aerobic capacity was shown to be of questionable validity as it was not consistent with the relative improvements in 6-Minute Walk Test distance on sitaxentan.

The third pivotal study, FPH04, was conducted in a different population of mainly non-Caucasian patients with a lesser disease severity (WHO functional class II). A smaller placebo-corrected improvement with sitaxentan 100 mg QD was noted in study FPH04 compared to studies FPH01 and FPH02, consistent with an assumption of disease severity-related efficacy. Across studies, sitaxentan 50 mg QD showed insufficient efficacy, while sitaxentan 300 mg QD showed no larger efficacy compared to sitaxentan 100 mg QD

Overall, the relative improvement in exercise capacity (6-Minute Walk Test distance) with sitaxentan 100 mg QD versus placebo appears to be clinically relevant, in view of a numerically comparable relative improvement observed with the previously licensed medicinal product bosentan. As expected in a rare disease, non-inferiority has not been formally demonstrated.

Sitaxentan's efficacy was generally consistent in subgroups according to sex, race, age, weight, and region. No reliable conclusions could be drawn in patients below 18 years of age, and as such treatment is not recommended under this age. The MAH has agreed to develop a clinical paediatric

programme to address the lack of safety and efficacy data. The data from the subgroup analyses did not provide compelling evidence for a clinically relevant treatment effect in patients with CHD-associated PAH that offsets the significant safety risk associated with sitaxentan, limiting the therapeutic indication to primary pulmonary arterial hypertension and PAH associated to connective tissue disease. A discrepancy between the expected baseline walking distance for patients in WHO functional class II and the reported mean baseline walking distance for patients in class II in the clinical programme was also observed. The findings raise doubts on the representativeness of the enrolled class II population for patients with class II disease severity in clinical practice. In addition, the improvement with sitaxentan 100 mg QD versus placebo in patients with WHO class II disease severity was small, and the conclusion reached was that the data do not allow WHO class II patients to be included in the therapeutic indication for sitaxentan.

Further supportive efficacy data were obtained from the long-term safety studies FPH01-X, FPH02-X and FPH03. Overall, these studies suggested maintenance of sitaxentan's efficacy up to 28 weeks of treatment.

Safety

Across all phase 2 and 3 studies in patients with PAH, 899 patients had been treated with sitaxentan with a mean exposure of 29 weeks.

The most common drug reactions considered to be at least possibly related to sitaxentan treatment were headache (15%), peripheral oedema (9%) and nasal congestion (9%).

Identified risks, appropriately addressed in the submitted Risk Management Plan, include hepatic toxicity, reductions in haemoglobin, bleeding events, teratogenicity, OATP interaction with sitaxentan sodium, and pulmonary oedema. The key safety issue is the hepatic toxicity. Cases of symptomatic hepatitis have occurred in patients receiving sitaxentan 100 mg once daily. As the effect of liver impairment on the pharmacokinetics is not clear and non-linear pharmacokinetics may result in disproportionately higher plasma concentrations of sitaxentan in patients with liver impairment, sitaxentan should not be used in patients with impaired liver function. The data suggest that the hepatotoxicity of sitaxentan is at a comparable level versus bosentan, although firm conclusions should not be drawn on the basis of these limited data obtained so far. The underlying mechanism of hepatotoxicity remains unclear at present. The SPC contains contra-indications, warnings, and strict monitoring plus stopping rules related to hepatic function. Also, sitaxentan will be distributed using a controlled access system and hepatotoxicity will be monitored in a post-marketing surveillance system.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

All the information has been appropriately translated into the package leaflet for which a user test has been adequately performed.

Risk-benefit assessment

The clinical programme evaluated the efficacy and safety of sitaxentan in a population of patients with mainly primary and connective tissue disease (CTD)-associated pulmonary arterial hypertension (PAH) at WHO functional class II and III. Overall, the relative improvement in exercise capacity (6-Minute Walk Test distance) with sitaxentan 100 mg QD versus placebo (~33 meters) is considered clinically relevant, in view of a numerically comparable relative improvement observed with the previously licensed medicinal product bosentan (30 meters) in a head-to-head comparison. As

expected in a rare disease, non-inferiority has not been formally demonstrated. The placebo-corrected improvement in the subgroup of patients dominated by those with WHO class III functional status was 46 meters. The findings were generally supported by results on the secondary endpoints change in WHO functional classification and rate on clinical worsening. However, the efficacy demonstrated in patients with WHO class II functional status and patients with CHD-associated PAH is considered insufficient.

The limited amount of patients included in the clinical trial programme for this orphan drug application has impact on the assessment of safety as these studies had low power to elucidate potential clinically relevant differences in the occurrence of less frequent events, such as serious adverse events and deaths. Although the incidence of death and serious adverse events with sitaxentan 100 mg QD relative to placebo and bosentan raised no major safety concern, any claim towards reduction of mortality in PAH patients treated according to the current standard of medical care remains unjustified given the limited sample size and the absence of clinical outcome studies. Accordingly, no such claims are made in the currently proposed SPC. Safety concerns exist regarding the occurrence of haemoglobin reductions and the potential for hepatotoxicity. Limited safety data suggested a reduced risk for aminotransferase elevations with sitaxentan 100 mg QD compared to bosentan under the protocol-specified monitoring and stopping rules for sitaxentan treated patients, but its clinical relevance remains to be established in the absence of a demonstration of a reduced risk for hepatic failure. Cases of symptomatic hepatitis have occurred in patients receiving sitaxentan 100 mg once daily. Some further safety concerns exist regarding the interaction with frequently used CYP2C9-dependent anticoagulants (e.g. warfarin, acenocoumarol) and associated bleeding events. These safety issues are addressed in the SPC and the Risk Management Plan.

Overall, the data suggest that oral sitaxentan 100 mg QD has a benefit/risk ratio comparable to the non-selective endothelin receptor antagonist bosentan. The benefit/risk ratio relative to other authorised medicinal products for the indication of PAH is difficult to assess, since no direct comparative data on clinical efficacy are available besides bosentan. Posology advantages apply over the indwelling catheter needed for continuous intravenous administration of epoprostenol (risk for infection and sepsis), the subcutaneous administration of treprostinil, and the frequent daily inhalations required for iloprost (6-9 times a day). No significant safety advantage over the oral medicinal product sildenafil would be expected given sitaxentan's potential for hepatotoxicity requiring strict monitoring. Given the difference in mechanism of action between the oral agents sitaxentan and sildenafil, a clinical study to evaluate the clinical efficacy and safety of co-administration was considered necessary.

It was concluded that sitaxentan sodium could be approvable for patients with primary pulmonary arterial hypertension and CTD-associated PAH in WHO/NYHA class III disease severity. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns, and the following additional risk minimisation activities were required:

Safety concern	**Proposed risk minimisation activities**
Use in Pediatric/adolescent patients	• Contraindication for children and adolescents under 18 years in section 4.3 of the SPC • Educational pack for physicians

Safety concern	Proposed risk minimisation activities
Hepatotoxicity	• Contraindication for patients with pre-existing hepatic disease (Child-Pugh Class A-C) and in patients with pre-treatment elevation of liver aminotransferases above 3 x ULN in section 4.3 of SPC. • Monthly monitoring of liver function with physicians requested to provide results via the proposed database. • Advice on treatment changes should aminotransferase levels rise above 3 x ULN but below 5 x ULN is provided in section 4.4 of the SPC. Treatment should be stopped immediately if aminotransferase levels rise above 5 x ULN. • Physicians and patients will receive educational material concerning sitaxentan sodium hepatotoxicity. • The pack size will be limited to 28 tablets.
Anaemia (decreases in haemoglobin and related red cell parameters)	• Physicians and patients will receive educational material concerning safety concern. • Haemoglobin concentrations are to be checked prior to treatment, after 1 and 3 months, and every 3 months thereafter. Physicians will be requested to provide results via the proposed database.
Teratogenicity	• Physicians and patients will receive educational material concerning safety concern. • The SPC (section 4.6 and 5.3) contains appropriate language concerning teratogenicity. • Treatment should not be initiated unless a woman is practicing reliable contraception. • The pack size will be limited to 28 tablets. • Need for negative pregnancy test prior to prescription.
Pre-existing hepatic disease or pre-treatment elevation of liver aminotransferases	• Dosage in hepatic impairment is covered in sections 4.2, 4.3 and 4.4 of the SPC (see hepatotoxicity).
Pulmonary oedema / pulmonary veno-occlusive disease	• Physicians will only be allowed to prescribe sitaxentan sodium after pre-certification training through the controlled access programme. • An appropriate warning will be included in section 4.4 of the SPC concerning the potential for this complication to occur.
Concomitant use of vitamin K antagonists	• Physicians will only be allowed to prescribe sitaxentan sodium after pre-certification training through the controlled access programme. • Appropriate guidance on vitamin K dosage adjustment is included in sections 4.4 and 4.5 of the SPC.
Co-administration with OATP Inhibitors	• Physicians and patients will receive educational material concerning sitaxentan sodium safety concerns. • Appropriate warnings included in sections 4.4 and 4.5 of the SPC.
Co-administration of ciclosporin A	• A contraindication is included in sections 4.3 and 4.5 of the SPC.

Safety concern	Proposed risk minimisation activities
Usage in combination with sildenafil and prostaglandins	• The effect of sitaxentan on sildenafil is included in section 4.5 • Spontaneous reports of adverse events will include recording of concomitant medications to allow the monitoring of safety of the concomitant use of sitaxentan sodium with sildenafil and prostaglandins through analysis of ADRs.
Potential for medication error	• Use of packaging design, colours and labelling to avoid any possible confusion with another product of a similar name

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Thelin is not similar to Tracleer, Ventavis or Revatio within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Thelin in the treatment of patients with primary pulmonary arterial hypertension and in pulmonary arterial hypertension associated with connective tissue disease, classified as WHO functional class III, to improve exercise capacity was favourable and therefore recommended the granting of the marketing authorisation.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Thelin not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Tracleer, Ventavis or Revatio for the same therapeutic indication.